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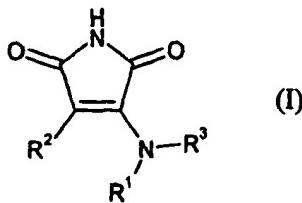
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(54) Title: PYRROLE-2,5-DIONE DERIVATIVES FOR THE TREATMENT OF DIABETES

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(57) Abstract: A method for the treatment of conditions associated with a need for inhibition of GSK-3, which method comprises the administration of a pharmaceutically effective, non-toxic amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof, wherein R¹ is a substituted or unsubstituted carbocyclic or heterocyclic aromatic ring, which ring may be fused to a substituted or unsubstituted carbocyclic or heterocyclic aromatic or non-aromatic ring; R² is a substituted or unsubstituted carbocyclic or heterocyclic aromatic ring, which ring may be fused to a substituted or unsubstituted carbocyclic or heterocyclic aromatic ring, with the proviso that R² is not 3-indolyl or a fused-ring derivative of 3-indolyl; R³ is hydrogen, or R¹ and R³ together with the nitrogen atom to which they are attached form a fused substituted or unsubstituted heterocyclic ring; to a human or non-human mammal in need thereof.

PYRROLE-2,5-DIONE DERIVATIVES FOR THE TREATMENT OF DIABETES

- This invention relates to a novel method for the treatment and/or prophylaxis of conditions associated with a need for inhibition of glycogen synthase kinase-3 (GSK-3), especially diabetes, and chronic neurodegenerative conditions including dementias such as Alzheimer's disease, neurotraumatic diseases such as acute stroke, manic depression, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, and immunodeficiency; and to certain novel inhibitors of GSK-3 for use in such a method.
- GSK-3 is a serine/threonine protein kinase composed of two isoforms (α and β) which are encoded by distinct genes. GSK-3 is one of several protein kinases which phosphorylates glycogen synthase (GS) (Embi *et al* Eur. J. Biochem. (107) 519-527 (1980)). The α and β isoforms have a monomeric structure and are both found in mammalian cells. Both isoforms phosphorylate muscle glycogen synthase (Cross *et al* Biochemical Journal (303) 21-26 (1994)) and these two isoforms show good homology between species (e.g. human and rabbit GSK-3 α are 96% identical).
- Type II diabetes (or Non-Insulin Dependent Diabetes Mellitus, NIDDM) is a multifactorial disease. Hyperglycaemia is due to insulin resistance in the liver, muscle and other tissues coupled with inadequate or defective secretion of insulin from pancreatic islets. Skeletal muscle is the major site for insulin-stimulated glucose uptake and in this tissue, glucose removed from the circulation is either metabolised through glycolysis and the TCA cycle, or stored as glycogen. Muscle glycogen deposition plays the more important role in glucose homeostasis and Type II diabetic subjects have defective muscle glycogen storage.
- The stimulation of glycogen synthesis by insulin in skeletal muscle results from the dephosphorylation and activation of glycogen synthase (Villar-Palasi C. and Larner J. Biochim. Biophys. Acta (39) 171-173 (1960), Parker P J *et al.*, Eur. J. Biochem. (130) 227-234 (1983), and Cohen P. Biochem. Soc. Trans. (21) 555-567 (1993)). The phosphorylation and dephosphorylation of GS are mediated by specific kinases and phosphatases. GSK-3 is responsible for phosphorylation and deactivation of GS, while glycogen bound protein phosphatase 1 (PP1G) dephosphorylates and activates GS. Insulin both inactivates GSK-3 and activates PP1G (Srivastava A K and Pandey S K Mol. and Cellular Biochem. (182) 135-141 (1998)).
- Chen *et al* Diabetes (43) 1234-1241 (1994) found that there was no difference in the mRNA abundance of PP1G between patients with Type II diabetes and control patients, suggesting that an increase in GSK-3 activity might be important in Type II diabetes. It has also recently been demonstrated that GSK-3 is overexpressed in Type II diabetic muscle and that an inverse correlation exists between skeletal muscle GSK-3 α activity and insulin action (Nikouline *et al* Diabetes 2000, 49 263-271). Overexpression of GSK-3 β and constitutively active GSK-3 β (S9A, S9E) mutants in HEK-293 cells resulted in suppression of glycogen synthase activity (Eldar-Finkelman *et al.*, PNAS (93) 10228-10233 (1996)) and overexpression of GSK-3 β in CHO cells, expressing both insulin receptor and insulin receptor substrate 1 (IRS-1), resulted in an impairment of insulin action (Eldar-Finkelman and Krebs PNAS (94) 9660-9664 (1997)). Recent evidence for the involvement of elevated GSK-3 activity and the development of insulin

resistance and type II diabetes in adipose tissue has emerged from studies undertaken in diabetes and obesity prone C57BL/6J mice (Eldar-Finkelman *et al.*, *Diabetes* **(48)** 1662-1666 (1999)).

5 GSK-3 has been shown to phosphorylate other proteins *in vitro* including the eukaryotic initiation factor eIF-2B at Serine⁵⁴⁰ (Welsh *et al.*, *FEBS Letts* **(421)** 125-130 (1998)). This phosphorylation results in an inhibition of eIF-2B activity and leads to a reduction in this key regulatory step of translation. In disease states, such as diabetes, where there is elevated GSK-3 activity this could result in a reduction of translation and potentially contribute to the pathology of the disease.

10 Several aspects of GSK-3 functions and regulation in addition to modulation of glycogen synthase activity indicate that inhibitors of this enzyme may be effective in treatment of disorders of the central nervous system. GSK-3 activity is subject to inhibitory phosphorylation by PI 3 kinase-mediated or Wnt-1 class-mediated signals that can be mimicked by treatment with lithium, a low mM inhibitor of GSK-3 (Stambolic V., 15 Ruel L. and Woodgett J.R. *Curr. Biol.* 1996 **6**(12): 1664-8).

15 GSK-3 inhibitors may be of value as neuroprotectants in treatment of acute stroke and other neurotraumatic injuries. Roles for PI 3-kinase signalling through PKB/akt to promote neuronal cell survival are well established, and GSK-3 is one of a number of PKB/akt substrates to be identified that can contribute to the inhibition of apoptosis via 20 this pathway (Pap & Cooper, (1998) *J. Biol. Chem.* **273**: 19929-19932). Evidence suggests that astrocytic glycogen can provide an alternative energy source to facilitate neuronal survival under conditions of glucose deprivation (for example see Ransom, B.R. and Fern, R. (1997) *Glia* **21**: 134-141 and references therein). Lithium is known to protect cerebellar granule neurons from death (D'Mello *et al.*, (1994) *Exp. Cell Res.* **211**: 25 332-338 and Volonte *et al* (1994) *Neurosci. Letts.* **172**: 6-10) and chronic lithium treatment has demonstrable efficacy in the middle cerebral artery occlusion model of stroke in rodents (Nonaka and Chuang, (1998) *Neuroreport* **9**(9): 2081-2084). Wnt-induced axonal spreading and branching in neuronal culture models has been shown to correlate with GSK-3 inhibition (Lucas & Salinas, (1997) *Dev. Biol.* **192**: 31-44) 30 suggesting additional value of GSK-3 inhibitors in promoting neuronal regeneration following neurotraumatic insult.

Tau and β-catenin, two known *in vivo* substrates of GSK-3, are of direct relevance in consideration of further aspects of the value of GSK-3 inhibitors in relation to treatment of chronic neurodegenerative conditions. Tau hyperphosphorylation is an early 35 event in neurodegenerative conditions such as Alzheimer's disease (AD), and is postulated to promote microtubule disassembly. Lithium has been reported to reduce the phosphorylation of tau, enhance the binding of tau to microtubules, and promote microtubule assembly through direct and reversible inhibition of glycogen synthase kinase-3 (Hong M., Chen D.C., Klein P.S. and Lee V.M. *J.Biol. Chem.* 1997 **272**(40) 40 25326-32). β-catenin is phosphorylated by GSK-3 as part of a tripartite complex with axin, resulting in β-catenin being targeted for degradation (Ikeda *et al.*, (1998) *EMBO J.* **17**: 1371-1384). Inhibition of GSK-3 activity is a key mechanism by which cytosolic levels of catenin are stabilised and hence promote β-catenin-LEF-1/TCF transcriptional activity (Eastman, Grosschedl (1999) *Curr. Opin. Cell Biol.* **11**: 233). Rapid onset AD 45 mutations in presenilin-1 (PS-1) have been shown to decrease the cytosolic β-catenin

pool in transgenic mice. Further evidence suggests that such a reduction in available β -catenin may increase neuronal sensitivity to amyloid mediated death through inhibition of β -catenin-LEF-1/TCF transcriptional regulation of neuroprotective genes (Zhang *et al.*, (1998) *Nature* **395**: 698-702). A likely mechanism is suggested by the finding that 5 mutant PS-1 protein confers decreased inactivation of GSK-3 compared with normal PS-1 (Weihs, C.C., Ghadge, G.D., Kennedy, S.G., Hay, N., Miller, R.J. and Roos, R.P. (1999) *J. Neurosci.* **19**: 5360-5369).

International Patent Application Publication Number WO 97/41854 (University of Pennsylvania) discloses that an effective drug for the treatment of manic depression is 10 lithium, but that there are serious drawbacks associated with this treatment. Whilst the precise mechanism of action of this drug for treatment of manic depression remains to be fully defined, current models suggest that inhibition of GSK-3 is a relevant target that contributes to the modulation of AP-1 DNA binding activity observed with this compound (see Manji *et al.*, (1999) *J. Clin. Psychiatry* **60** (suppl 2): 27-39 for review).

15 GSK-3 inhibitors may also be of value in treatment of schizophrenia. Reduced levels of β -catenin have been reported in schizophrenic patients (Cotter D, Kerwin R, al-Sarraji S, Brion JP, Chadwick A, Lovestone S, Anderton B, and Everall I. 1998 *Neuroreport* **9**:1379-1383) and defects in pre-pulse inhibition to startle response have been observed in schizophrenic patients (Swerdlow *et al* (1994) *Arch. Gen. Psychiat.* **51**: 20 139-154). Mice lacking the adaptor protein dishevelled-1, an essential mediator of Wnt-induced inhibition of GSK-3, exhibit both a behavioural disorder and defects in pre-pulse inhibition to startle response (Lijam N, Paylor R, McDonald MP, Crawley JN, Deng CX, Herrup K, Stevens KE, Maccaferri G, McBain CJ, Sussman DJ, and Wynshaw-Boris A. (1997) *Cell* **90**: 895-905). Together, these findings implicate deregulation of GSK-3 25 activity as contributing to schizophrenia. Hence, small molecule inhibitors of GSK-3 catalytic activity may be effective in treatment of this mood disorder.

The finding that transient β -catenin stabilisation may play a role in hair development (Gat *et al* *Cell* (95) 605-614(1998)) suggests that GSK-3 inhibitors could be used in the treatment of baldness.

30 Studies on fibroblasts from the GSK-3 β knockout mouse (Hoeflich KP *et al.*, *Nature* 2000, **406**, 86-90) support a role for this kinase in positively regulating the activity of NFkB. This transcription factor mediates cellular responses to a number of inflammatory stimuli. Therefore, pharmacologic inhibition of GSK-3 may be of use in treating inflammatory disorders through the negative regulation of NFkB activity.

35 International Patent Application Number WO 98/16528 (Chiron Corporation) discloses certain purine derivatives as GSK-3 inhibitors. WO 99/47522 (University of British Columbia) discloses certain granulatimide derivatives as GSK-3 β inhibitors. WO 99/65897 (Chiron Corporation) discloses certain pyrimidine and pyridine derivatives as GSK-3 inhibitors. WO 00/17184 (Mitsubishi Chemical Corporation) discloses certain 40 hydroflavone derivatives as Tau protein kinase-1 (TPK-1) inhibitors, where Tau protein kinase is a synonym for GSK-3 β . Co-pending International Patent Application No. WO 00/18758 Mitsubishi Chemical Corporation) discloses certain pyrimidone derivatives as TPK-1 inhibitors. Co-pending International Patent Applications Nos. WO 00/21927 and WO 00/38675 disclose certain pyrrole-2,5-dione derivatives as GSK-3 inhibitors. Co-

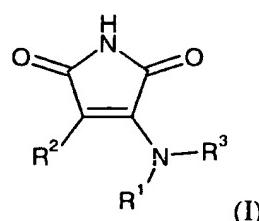
pending International Patent Application No. WO 01/09106 (SmithKline Beecham Plc) discloses certain 1,2,4-triazole derivatives as GSK-3 inhibitors.

Certain substituted 3-amino-4-arylmaleimides are disclosed in *J Amer Chem Soc* 1958, 80, 1385 which compounds have no disclosed pharmaceutical utility.

5 WO 00/06564 (Japan Tobacco Inc.) discloses certain 3-amino-4-(3-indolyl) maleimide derivatives as PKC-beta inhibitors.

We have now discovered that a series of 3-amino-4-arylmaleimides are particularly potent and selective inhibitors of GSK-3. These compounds are indicated to be useful for the treatment and/or prophylaxis of conditions associated with a need for
10 inhibition of GSK-3, such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and manic depression, hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, inflammation and immunodeficiency.
15

Accordingly, in a first aspect, the present invention provides a method for the treatment of conditions associated with a need for inhibition of GSK-3, such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, neurotraumatic diseases such as acute stroke,
20 mood disorders such as schizophrenia and manic depression, hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, inflammation and immunodeficiency, which method comprises the administration of a pharmaceutically effective, non-toxic amount of a compound of formula (I):
25



or a pharmaceutically acceptable derivative thereof,
wherein;

30 R¹ is a substituted or unsubstituted carbocyclic or heterocyclic aromatic ring, which ring may be fused to a substituted or unsubstituted carbocyclic or heterocyclic aromatic or non-aromatic ring;

35 R² is a substituted or unsubstituted carbocyclic or heterocyclic aromatic ring, which ring may be fused to a substituted or unsubstituted carbocyclic or heterocyclic aromatic ring, with the proviso that R² is not 3-indolyl or a fused-ring derivative of 3-indolyl;

R³ is hydrogen, or,

R¹ and R³ together with the nitrogen atom to which they are attached form a fused substituted or unsubstituted heterocyclic ring;

to a human or non-human mammal in need thereof.

When R¹ is a substituted or unsubstituted carbocyclic aromatic ring, examples include phenyl.

- 5 When R¹ is a substituted or unsubstituted heterocyclic aromatic ring, examples include pyridinyl.

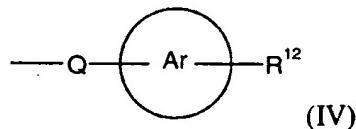
When R¹ is a substituted or unsubstituted carbocyclic aromatic ring which ring is fused to a substituted or unsubstituted carbocyclic non-aromatic ring, examples include indanyl.

- 10 When R¹ is a substituted or unsubstituted carbocyclic aromatic ring which ring is fused to a substituted or unsubstituted heterocyclic aromatic or non-aromatic ring, examples include benzothiazolyl, benzoxazolyl, indolinyl, quinolinyl, indolyl, benzothiazolinonyl, benzimidazolyl, benzimidazolinonyl, benzothiophenyl, benzofuranyl, indolinonyl, benzoxazinonyl, and benzoxazolinonyl.

- 15 When R² is a substituted or unsubstituted carbocyclic aromatic ring, examples include phenyl.

When R¹ and R³ together with the nitrogen atom to which they are attached form a fused substituted or unsubstituted heterocyclic ring, examples include indolinyl and tetrahydroquinolinyl.

- 20 When R¹ is a substituted carbocyclic aromatic ring or a substituted heterocyclic aromatic ring, suitable substituents include up to five groups independently selected from the list consisting of hydroxy, C₁-6alkoxy, di-(C₁-6alkyl)amino, cyano, substituted or unsubstituted C₁-6alkyl, carboxy, C₁-6alkoxycarbonyl, C₁-6alkylaminocarbonyl, halo, carboxyC₁-6alkyloxy, C₁-6alkylamino, morpholinyl, hydroxyC₁-6alkylaminocarbonyl, (di-C₁-6alkylamino)carbonyl, C₁-6alkoxyC₁-6alkylaminosulphonyl, C₁-6alkylaminosulphonyl, C₁-6alkylcarbonyl, C₁-6alkylcarbonylamino, (perfluoroC₁-6alkyl)carbonylamino, C₁-6alkylthio, amino, perfluoroC₁-6alkyl, aminocarbonyl, nitro, aminocarbonylC₂-6alkenyl, C₁-6alkoxyC₁-6alkylcarbonylamino, C₁-6alkoxycarbonylC₁-6alkylcarbonylamino, hydroxyC₁-6alkylcarbonylamino, C₁-6alkoxycarbonylC₁-6alkylcarbonylamino, carboxyC₁-6alkylcarbonylamino, 30 aminosulphonyl, carboxyC₂-6alkenyl, aminocarbonylC₁-6alkylcarbonylamino, C₁-6alkylaminocarbonylC₁-6alkoxy, phenoxy, carboxyC₁-6alkyl, carboxycarbonylamino, thiazolidindionylC₁-6alkyl, C₁-6alkylcarbonylhrazocarbonylC₁-6alkyl, C₁-6alkylcarbonylaminoC₁-6alkyl, C₁-6alkylsulphonylaminoC₁-6alkyl, (C₁-6alkyloxy)hydroxyphosphinylC₁-6alkyl, aminosulphonylC₁-6alkyl, C₁-6alkoxyaminocarbonylC₁-6alkyl, hydroxyaminocarbonylC₁-6alkyl, C₁-6alkoxyaminocarbonylC₂-6alkenyl, aminoC₁-6alkyl, and moiety (IV)



- 40 wherein;

Q is a bond or a bivalent linking group;

Ar represents a carbocyclic or heterocyclic aromatic ring;

R¹² represents hydrogen or one or more substituent, suitably up to five,

independently selected from the list consisting of carboxyC₂-6alkenyl, C₁-

- 5 6alkylcarbonylamino, amino, C₁-6alkylamino, (di-C₁-6alkyl)amino, halo, cyano, C₁-
6alkoxy, C₁-6alkoxycarbonyl, (di-C₁-6alkyl)aminocarbonyl, carboxyC₁-6alkyl, C₁-
6alkylaminocarbonyl, carboxy, hydroxy, aminocarbonyl, C₁-6alkoxyC₁-
6alkylaminocarbonyl, C₁-6alkylaminocarbonylC₁-6alkyl, morpholinylC₁-
6alkylaminocarbonylC₁-6alkyl, C₁-6alkyl, aminocarbonylC₁-6alkyl,
hydroxyaminocarbonylC₁-6alkyl, C₁-6alkoxycarbonylC₁-6alkyl, phenyl, hydroxyC₁-
10 6alkyl, morpholinyl, piperidinyl, cyanoC₁-6alkyl, (C₁-6alkylpiperidinyl)C₁-6alkoxy,
(C₁-6alkylcarbonyl)(C₁-6alkyl)amino, C₁-6alkylcarbonylaminoC₁-6alkyl, (di-C₁-
6alkyl)aminoC₁-6alkyl, aminosulphonyl, ureido, and C₁-6alkylsulphonylamino.

When Ar is a carbocyclic aromatic ring, examples include phenyl.

When Ar is a heterocyclic aromatic ring, examples include oxazolyl,

- 15 benzothiazolyl, quinoliny, oxadiazolyl, pyrimidinyl, pyrazinyl, dihydropyridazinonyl,
pyrazolyl, imidazolyl, pyrazinonyl, dihydro-oxadiazinonyl, pyridazinonyl, and pyridinyl.

Examples of Q include -[CONH], -[(CH₂)₁₋₆O]-, -[CONH(CH₂)₁₋₆]-, -[(CH₂)₁₋₆CONH(CH₂)₁₋₆]-, -[S]-, -[O]-, -[(CH₂)₁₋₆CONH]-, -[CO]-, -[O(CH₂)₁₋₆]-, -[NHCO]-, -[NHSO₂]-, -[(CH₂)₁₋₆NHCO(CH₂)₁₋₆]-, -[SO₂NH]-, -[(CH₂)₁₋₆NHSO₂(CH₂)₁₋₆]-, -[NHCO(CH₂)₁₋₆]-, a bond, -[(CH₂)₁₋₆NHCO]-, -[(CH₂)₁₋₆NHSO₂]-, -[NH]-, -[CH₂O]-, -[(CH₂)₁₋₆SO₂NH]-, -[(CH₂)₁₋₆CO₂(CH₂)₁₋₆SO₂]-, -[(CH₂)₁₋₆CONHNHCO]-, -[(CH₂)₁₋₆CO₂(CH₂)₁₋₆]-, -[O(CH₂)₁₋₆N(C₁-6alkyl)]-, -[S(CH₂)₁₋₆]-, and -[SO₂]-.

- 20 Suitable substituents for any alkyl group include cyano, C₁-6alkylaminocarbonyl,
aminosulphonyl, C₁-6alkoxy, C₁-6alkylsulphonylamino, hydroxy, carboxy,
phenylaminocarbonyl, phenylC₁-6alkylaminocarbonyl, phenylcarbonylamino, phenylC₁-
6alkylcarbonylamino, thiazolidinedionyl, piperazinylcarbonyl where the piperazinyl
group may be substituted or unsubstituted, morpholinylcarbonyl, piperidinylcarbonyl,
hydroxyC₁-6alkylaminocarbonyl, (di-C₁-6alkylamino)carbonyl, C₁-
6alkylaminosulphonyl, aminocarbonyl, (di-C₁-6alkylamino)C₁-6alkylaminocarbonyl,
C₁-6alkoxycarbonylamino, C₁-6alkylcarbonylamino, C₁-6alkoxyC₁-
6alkylcarbonylamino, C₁-6alkylcarbonylaminoC₁-6alkylcarbonylamino, C₁-
6alkoxycarbonylC₁-6alkylcarbonylamino, hydroxyC₁-6alkylcarbonylamino, and (di-C₁-
6alkylamino)sulphonyl.

- 25 35 Suitable substituents for any piperazinyl group include C₁-6alkyl.

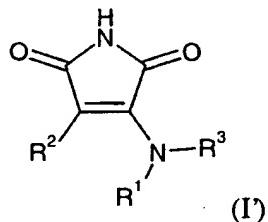
Suitably, R¹ is unsubstituted phenyl or phenyl substituted with:

- 4-[S-(3-CH₂CO₂H)Ph], 4-[S-(3-CONHMe)Ph], 4-[O-(3-CO₂H)Ph], 3-CO₂H, 3-[
CH₂CONHPh], 4-[CH₂CONHPh], 3-COPh, 3-OCH₂Ph, 4-[NHCO-(2-OH)Ph], 3-
CO₂Et, 4-[S-(2-CO₂H)Ph], 4-[O-(3-CONHMe)Ph], 4-[O-(3-CONH₂)Ph], 4-[S-(3-
CONH₂)Ph], 4-[O-(4-CONHMe)Ph], 4-[NHCOPh], 4-[S-[3-CONH(CH₂)₂OMe]Ph], 4-[
S-(2-CO₂H)Ph], 4-[NHCOCH₂Ph], 3-[NHCOCH₂Ph], 3-CONHPh, 4-[O-(4-CO₂H)Ph],
4-SPh, 4-[CH₂NHCOCH₂Ph], 3-CONHMe, 4-[O-(4-CONH₂)Ph], 4-[S-(3-
CH₂CONHMe)Ph], 4-[S-[3-CH₂CONH(CH₂)₂(morpholin-4-yl)]Ph], 3-SO₂NHPh, 3-
CH₂NHCOPh, 4-[NHSO₂(4-Me)Ph], 3-CH₂NHCOCH₂Ph, 4-[NHCO(CH₂)₂Ph], 4-[S-

- (3-CH₂CONH₂)Ph], 4-[S-(3-CO₂H)Ph], 4-[S-(3-CH₂CONHOH)Ph], 4-[O-(2-CO₂H)Ph], 4-Ph, 4-[S-(2-CH₂CO₂Me)Ph], 4-[S-(4-CONH₂)Ph], 4-[S-(4-CO₂H)Ph], 4-[O-(2-CONHMe)Ph], 4-[CH₂CONH-(3-CO₂H)Ph], 4-[O-(3-CH₂CO₂H)Ph], 4-[S-(2-CO₂H)Ph], 4-[O-(2-CONH₂)Ph], 3-[CH₂(1,3-thiazolidine-2,4-dion-5-yl)], 3,5-di-F, 3-Cl,
- 5 3-OCH₂CO₂H, 3-CONHMe-4-NHMe, 4-[CH₂CO(4-Me-piperazin-1-yl)], 2-[morpholin-4-yl], 3-[CH₂CO(morpholin-4-yl)], 3-[CH₂CO(piperidin-1-yl)], 4-[CH₂CO(piperidin-1-yl)], 4-[CH₂CONH(CH₂)₂OH], 4-[CH₂CONMe₂], 3-[CONHMe]-4-Cl, 3-SO₂NH(CH₂)₂OMe, 3-SO₂NHn-Bu, 3-COME, 3-CH₂CO₂H, 3-NHCOMe, 4-NHCOCF₃, 2-Me, 2-Me-4-F, 2-Me-5-F, 3-Me, 2-SMe, 3-CF₃-4-NH₂, 3-CF₃-4-
- 10 NHCOMe, 4-CH₂SO₂NHMe, 4-CH₂CH₂CONH₂, 4-Me, 3-[CH₂CONH(CH₂)₂NMe₂], 4-NH₂, 3-NO₂, 3-NH₂, 2,3,4-tri-F, 3-F-5-CF₃, 4-[O(CH₂)₃CO₂H], 4-CH₂NHCO₂t-Bu, trans-4-[CH=CHC(O)NH₂], 4-[NHCOC₂OMe], 4-[NHCOC₂NHCOMe], 4-CH₂NHCO_n-Pr, 4-[NHCOC₂OH], 3-[NHCOC₂OMe], 4-[NHCOC₂CO₂t-Bu], 3-[NHCOC₂NHC(O)Me], 4-[NHCO_n-Pr], 4-[NHCOC₂CO₂H], 4-
- 15 [CH₂NHCO₂OMe], 4-[CH₂NHCO₂NHCOMe], 4-[(CH₂)₃CO₂H], 3-[CH₂NHCO₂t-Bu], 4-[CH₂NHCO₂OH], 4-[NHCOC₂OH], 3-OH-4-[NHCOC₂OMe], 4-[CH₂NHCO₂CO₂t-Bu], 3-[CH₂CONH₂], 3-[SO₂NH₂], 3-[CH₂NHCO₂OMe], 3-[CH₂NHCO₂NHCOMe], 3-[CH₂NHCO₂OH], trans-4-[CH=CHCO₂H], 4-[NHCO(CH₂)₂CONH₂], 4-O(CH₂)₃CONHMe, 4-[NHCOC₂OMe], 4-
- 20 [CH₂SO₂NHMe], 4-[CH₂SO₂NMe₂], 3-[CH₂CONH₂], 4-[CH₂SO₂NHMe], 4-[CH₂(1,3-thiazolidine-2,4-dion-5-yl)], 3-[oxazol-5-yl], 4-[NHCO(CH₂)₂(3-pyridinyl)], 4-[5-Me-2-oxazolyl], 4-[2-Me-4-oxazolyl], 4-[S-(2-CONH₂)Ph], 4-[S-(2-CONHMe)Ph], 4-[CH₂CONH-(4-CO₂H)Ph], 3-[CH₂CONH-(4-CO₂H)Ph], 3-CO₂H-4-[O-Ph], 3-CO₂H-4-[O-(4-Ph)Ph], 3-[CONH-(4-CO₂H)Ph], 3-[CH₂O-(4-CO₂H)Ph], 4-
- 25 [CH₂SO₂NH-Ph], 4-[O-(4-CO₂H)Ph], 3-[O-(4-CO₂H)Ph], 3-[O-(4-CH₂CO₂H)Ph], 4-[O-(4-CH₂CO₂H)Ph], 3-[CH₂CONH-(4-CH₂CH₂OH)Ph], 3-[O-(3-CO₂H)Ph], 3-[O-(4-CH₂CH₂CO₂H)Ph], 3-[CH₂CONH-(4-(morpholin-4-yl)Ph)], 3-[CH₂CONH-(4-(piperidin-1-yl)Ph)], 3-[CH₂CONH-(4-CH₂OH)Ph], 4-[O-(3-NMe₂)Ph], 3-[OCH₂-(4-CO₂H)Ph], 3-[CH₂CO₂CH₂CH₂SO₂-(4-NH₂)Ph], 3-[CH₂CONH-(4-NMe₂)Ph], 3-
- 30 [CH₂CONH-(3-Cl-4-(morpholin-4-yl)Ph)], 3-[CH₂CONH-(4-CH₂CN)Ph], 3-[CH₂CONH-4-(OCH₂(1-methylpiperidin-4-yl)Ph)], 3-[O-(3-NH₂)Ph], 4-[O-4-NHCOMe)Ph], 3-Me-4-[O-(4-CH₂CO₂H)Ph], 4-[CH₂SO₂NH-(4-CO₂H)Ph], 4-[O-(3-NHCOMe)Ph], 3-[CH₂CONH-(3-NHCOMe)Ph], 3-[CH₂CONH-(4-NHCOMe)Ph], 3-[CH₂CONH-(4-N(Me)COMe)Ph], 3-[CH₂CONH-(3-CONH₂)Ph], 3-[CH₂CONH-(2-CONH₂)Ph], 3-[CH₂CONH-(3-NMe₂)Ph], 4-[CH₂SO₂NH-(4-CH₂CO₂H)Ph], 4-[CH₂SO₂NH-(3-CH₂CO₂H)Ph], 4-[CH₂SO₂NH-(3-CO₂H)Ph], 3-Cl-4-[O-(4-CH₂CO₂H)Ph], 3-Cl-4-[O-(4-CO₂H)Ph], 3-[CH₂CONH-(3-CO₂H)Ph], 3-[CH₂CONHCH₂-(4-NMe₂)Ph], 3-[CH₂CONHNHCO-(4-NH₂)Ph], 4-[O-(4-CH₂NHCOMe)Ph], 3-CO₂H-4-[O-(4-Cl)Ph], 3-[O-(4-NHCOMe)Ph], 3-[CH₂CONH-(4-CONH₂)Ph], 4-[O-(3-NHCONH₂)Ph], 4-[O-(4-CH₂CH₂NMe₂)Ph], 3-[CH₂CONH-(3-NH₂)Ph], 3-[CH₂CONH-(4-NH₂)Ph], 3-[CH₂CONHNHCO-Ph], 3-[CH₂CONH-(4-SO₂NH₂)Ph], 3-[CH₂CONH-(3-CH₂OH)Ph], 3-[CH₂CONH(CH₂)₂-(4-NH₂)Ph], 3-[CH₂CONHNHCO-(3-NH₂)Ph], 3-[CH₂SO₂NH-Ph], 3-[CH₂SO₂NH-(3-CO₂H)Ph], 3-[CH₂CONH-(4-NHSO₂Me)Ph], 3-[CH₂SO₂NH-(4-CO₂H)Ph], 3-[SO₂-(3-NH₂)Ph], 4-
- 40 -7-

- [O-(4-SO₂NH₂)Ph], 4-[O-(4-NH₂)Ph], 4-[CH₂SO₂NH-(4-NHSO₂Me)Ph], 4-[CH₂SO₂NH-(4-NHCOMe)Ph], 4-[6-Me-2-benzothiazolyl], 4-[O-(3-pyridinyl)], 3-[2-benzothiazolyl], 3-[CH₂CONH(3-quinolinyl)], 4-[3-Me-1,2,4-oxadiazol-5-yl], 3-[CH₂CONH(2-Me-pyridin-3-yl)], 3-[CH₂CONH(5-Me-pyridin-3-yl)], 3-[CH₂CONH(2-
- 5 OMe-pyridin-5-yl)], 3-[CH₂CONH(pyridin-3-yl)], 3-[CH₂CO₂CH₂(3-NH₂-pyridin-2-yl)], 4-[O(CH₂)₂NMe(pyridin-2-yl)], 4-[OCH₂(pyridin-3-yl)], 3-[CH₂CONH(pyrimidin-4-yl)], 3-[CH₂CONH(pyrazin-2-yl)], 4-[O-(pyridin-2-yl)], 4-[2-OH-pyrimidin-5-yl)], 4-[5-Me-4,5-dihydro-2H-pyridazin-3-on-6-yl)], 4-[2,5-di-Me-4,5-dihydro-2H-pyridazin-3-on-6-yl)], 4-[1H-pyrazol-3-yl], 4-[SCH₂(1H-imidazol-4-yl)], 3-[CH₂SO₂NH(pyridin-3-yl)], 4-[2-OMe-pyrazin-5-yl)], 4-[1H-pyrazin-2-on-5-yl)], 4-[5,6-dihydro-4H-[1,3,4]-oxadiazin-5-on-2-yl)], 4-[4,5-dihydro-2H-pyridazin-3-on-6-yl)], 4-[2H-pyridazin-3-on-6-yl)], 3-CH₂CH₂CO₂H, 4-CH₂CH₂CH₂CO₂H, 4-CH₂CH₂CH₂CO₂H, 4-OH, 3,5-di-Cl-4-OH, 4-(CH₂)₂CO₂H, 3-F-4-OCH₂CO₂H, 4-NHCOCO₂H, 3-Me-4-trans-CH=CHCO₂H, 3-CH₂CONHNHCOMe, 4-(CH₂)₄NHCOMe, 4-(CH₂)₄NHSO₂Me, 3-
- 10 CH₂NHSO₂Me, 4-CH₂CH₂P(O)(OEt)OH, 4-CH₂CH₂SO₂NH₂, 3-CH₂SO₂NH₂, 3-CH₂CONHOMe, 3-CH₂CONHOH, 4-trans-CH=CHCONHOMe, 4-CH₂NH₂, or 3-CH₂NH₂.
- Favourably, R¹ is phenyl substituted with 4-[S-(3-CH₂CO₂H)Ph].
- Suitably, R¹ is pyridin-5-yl substituted with 2-[(CH₂)₃CN]-3-Me, 2-[(CH₂)₂CO₂H]-, 2-[(CH₂)₄CO₂H]-, 2-[(CH₂)₃CN]-3-CO₂Et, or 2-[OPh].
- Suitably, R¹ is pyridin-3-yl substituted with 2-Me, or 2-[(CH₂)₃CN].
- When R¹ is a substituted or unsubstituted carbocyclic aromatic ring which ring is fused to a substituted or unsubstituted heterocyclic aromatic or non-aromatic ring, suitable substituents for either ring include carboxyC₁-6alkylthio and esters thereof, halo, aminocarbonyl, hydroxy, aryloxy, arylthio, arylamino, C₁-6alkyl, C₁-6alkylcarbonyl, C₁-6alkylsulphonyl, C₁-6alkylthio, C₁-6alkoxy, C₁-6alkoxycarbonyl, carboxy, carboxyC₁-6alkyl, substituted or unsubstituted aryl, arylC₁-6alkyl, amino, di-(C₁-6alkyl)amino, di-(C₁-6alkyl)aminoC₁-6alkyl, C₁-6alkoxycarbonylC₁-6alkyl, di-(C₁-6alkyl)aminoC₁-6alkylamino, morpholinyl, C₁-6alkylcarbonylamino, and C₁-6alkylamino.
- Suitably, R¹ is indolin-5-yl unsubstituted or substituted with 1-(SO₂Me), or 1-CO₂t-Bu.
- Suitably, R¹ is indan-5-yl.
- Suitably, R¹ is quinolin-6-yl.
- Suitably, R¹ is indol-5-yl unsubstituted or substituted with [1-Me-2-CONH₂], 1-Me, or [1-Me-2-CO₂H].
- Suitably, R¹ is benzoxazol-5-yl substituted with 2-Me.
- Suitably, R¹ is unsubstituted benzoxazol-6-yl, or benzoxazol-6-yl substituted with 2-Me.
- Suitably, R¹ is benzothiazol-5-yl substituted with 2-Me.
- Suitably, R¹ is unsubstituted benzothiazol-6-yl or benzothiazol-6-yl substituted with 2-[NHCOMe], 2-NH₂, 2-NHiPr, 2-[NHEt], 2-[morpholin-4-yl], 2-[NH(CH₂)₃N(Me)₂], 2-[(CH₂)₄CO₂H], 2-[(CH₂)₄CO₂Me], 2-NHPh, 2-[S(CH₂)₃CO₂H], 2-Ph, 2-NHMe, 2-N(Me)₂, 2-Cl, 2-SMe, 2-Me, 2-(SCH₂CO₂Me), or 2-(SCH₂CO₂H).

- Suitably, R¹ is benzthiazolinon-6-yl unsubstituted or substituted with 3-CH₂CO₂Me, 3-[3-F-Ph], 3-[4-OMe-Ph], 3-[CH₂Ph], 3-[3-NHCOMe-Ph], 3-[CH₂)₃N(Me)₂], 3-Me, 3-CH₂CO₂H.
- 5 Suitably, R¹ is benzoxazolinon-6-yl.
- 5 Suitably, R¹ is benzoxazolinon-5-yl.
- 5 Suitably, R¹ is benzimidazol-5-yl substituted with 2-Me.
- 5 Suitably, R¹ is benzimidazolinon-5-yl unsubstituted or substituted with 1,3-di-Me
- 5 Suitably, R¹ is benzothiophen-5-yl.
- 5 Suitably, R¹ is benzofuran-5-yl substituted with 2-CO₂H.
- 10 Suitably, R¹ is indolin-2-on-5-yl.
- 10 Suitably, R¹ is 2H-1,4-benzothiazin-3(4H)-on-7-yl.
- 10 Favourably, R¹ is unsubstituted benzoxazolinon-6-yl.
- 10 Favourably, R¹ is unsubstituted benzthiazolinon-6-yl.
- 10 Favourably, R¹ is unsubstituted indolin-2-on-5-yl.
- 15 Favourably, R¹ is benzothiazol-6-yl substituted with a 2-amino group.
- 15 When R² is a substituted carbocyclic or heterocyclic aromatic ring, suitable substituents include up to five groups independently selected from the list consisting of hydroxyC₁-6alkyl, carboxy, cyano, aminocarbonyl, halo, C₁-6alkoxy, nitro, perfluoroC₁-6alkyl, benzoyl, C₁-6alkoxycarbonyl, C₁-6alkylsulphonyl, hydroxy, -O(CH₂)_wO- where
- 20 w is 1 to 4, phenoxy, benzyloxy, C₁-6alkoxyC₁-6alkyl, perfluoroC₁-6alkoxy, C₁-6alkylS-, perfluoroC₁-6alkylS-, (diC₁-6alkyl)N-, amino, C₁-6alkylcarbonylamino, substituted or unsubstituted ureido, phenylcarbonylamino, benzylcarbonylamino, styrylcarbonylamino, C₁-6alkyl, and phenyl.
- 25 Suitable substituents for ureido include fluorophenyl, phenylC₁-6alkyl-, cyclohexyl, C₁-6alkenyl, C₁-6alkyl, and C₁-6alkoxyphenyl.
- 25 Suitably, R² is unsubstituted phenyl or phenyl substituted with 4-NO₂, 4-NHCOMe, 4-I, 2,3-di-F, 3-CN, 2,3,6-tri-F, 3-CO₂H, 3-CH₂OH, 2,3,5-tri-F, 3,5-di-Me, 3-F, 2-Cl-5-F, 2-Cl, 2-F-3-Cl, 2-Cl-3-F, or 4-Cl.
- 30 Favourably, R² is phenyl substituted with 2,3-di-F.
- 30 When R¹ and R³ form substituted indolinyl, suitable substituents include hydroxyC₁-6alkyl and C₁-6alkoxyC₁-6alkyl.
- 30 Suitably, R¹ and R³ form indolinyl substituted with 2-(hydroxymethyl) or 2-(methoxymethyl).
- 35 Suitably, R¹ and R³ form tetrahydroquinolinyl.
- 35 Preferred compounds of formula (I) are selected from the list consisting of Example A1 in Table A, and Example B10, Example B16, Example B47, and Example B49 in Table B.
- 35 There is a sub-group of compounds, falling wholly within formula (I), and being of formula (I')
- 40

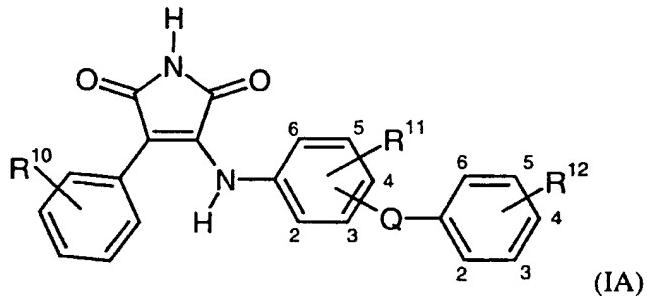


wherein;

- R¹, R², and R³ are as defined in formula (I), with the proviso that formula (I)
 5 does not include the following compound:
 3-phenylamino-4-phenyl-1H-pyrrole-2,5-dione.
- It is considered that the compounds of formula (I') are novel. Accordingly, the present invention also provides a compound of formula (I') or a derivative thereof.

Preferred compounds of formula (I') are selected from the list consisting of
 10 Example A1 in Table A, and Example B10, Example B16, Example B47, and Example B49 in Table B.

There is a subgroup of compounds falling wholly within formula (I') being of formula (IA)



15

wherein;

R¹⁰ represents hydrogen or one or more substituents, suitably up to five, independently selected from the list consisting of halo and cyano;

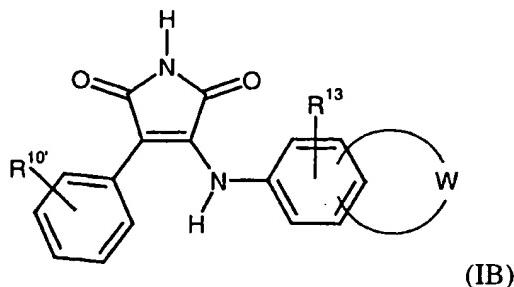
20 R¹¹ represents hydrogen or one or more substituents, suitably up to four, independently selected from the list consisting of carboxy, C₁-6alkoxycarbonyl, C₁-6alkylaminocarbonyl, halo, and C₁-6alkyl;

Q represents a bond or a bivalent linking group.

Examples of Q include -[CONH]-, -[(CH₂)₁₋₆O]-, -[CONH(CH₂)₁₋₆]-, -[(CH₂)₁₋₆CONH]-, -[CO]-, -[O(CH₂)₁₋₆]-, -[NHCO]-, -[NHSO₂]-, -[(CH₂)₁₋₆NHCO(CH₂)₁₋₆]-, -[SO₂NH]-, -[(CH₂)₁₋₆NHSO₂(CH₂)₁₋₆]-, -[NHCO(CH₂)₁₋₆]-, a bond, -[(CH₂)₁₋₆NHCO]-, -[(CH₂)₁₋₆NHSO₂]-, -[NH]-, -[(CH₂)₁₋₆SO₂NH]-, -[(CH₂)₁₋₆CO₂(CH₂)₁₋₆SO₂]-, -[(CH₂)₁₋₆CONHNHCO]-, and -[SO₂]-.

30 R¹² represents hydrogen or one or more substituents, suitably up to five, independently selected from the list consisting of C₁-6alkylcarbonylamino, amino, C₁-6alkylamino, (di-C₁-6alkyl)amino, halo, cyano, C₁-6alkoxy, C₁-6alkoxycarbonyl, (di-

- C_{1-6} alkyl)aminocarbonyl, hydrogen, carboxy C_{1-6} alkyl, C_{1-6} alkylaminocarbonyl, carboxy, hydroxy, aminocarbonyl, C_{1-6} alkoxy C_{1-6} alkylaminocarbonyl, C_{1-6} alkylaminocarbonyl C_{1-6} alkyl, morpholinyl C_{1-6} alkylaminocarbonyl C_{1-6} alkyl, C_{1-6} alkyl, aminocarbonyl C_{1-6} alkyl, hydroxyaminocarbonyl C_{1-6} alkyl, C_{1-6}
- 5 $alkoxycarbonylC_{1-6}$ alkyl, phenyl, hydroxy C_{1-6} alkyl, morpholinyl, piperidinyl, cyano C_{1-6} alkyl, (methylpiperidinyl) C_{1-6} alkoxy, (C_{1-6} alkylcarbonyl)(C_{1-6} alkyl)amino, C_{1-6} alkoxyamino C_{1-6} alkyl, (di- C_{1-6} alkyl)amino C_{1-6} alkyl, aminosulphonyl, C_{1-6} alkylcarbonylamino C_{1-6} alkyl, ureido, and C_{1-6} alkylsulphonylamino.
- Suitably, R^{10} represents hydrogen, 2,3-di-F, 3-CN, 2-F-3-Cl, 2,3,6-tri-F, 2-Cl-3-
- 10 F, and 4-Cl.
- Favourably, R^{10} represents 2,3-di-F.
- Suitably, R^{11} represents hydrogen, 3-CO₂H, 3-CO₂Et, 3-CONHMe, 3-Me, or 3-Cl.
- Suitably, Q represents 4-[S]-, 4-[O]-, 3-[CH₂CONH]-, 4-[CH₂CONH]-, 3-[CO]-,
- 15 3-[OCH₂]-, 4-[NHCO]-, 4-[NHCOCH₂]-, 3-[NHCOCH₂]-, 3-[NHCO]-, 4-[CH₂NHCOCH₂]-, 3-[SO₂NH]-, 3-[CH₂NHCO]-, 4-[NHSO₂]-, 3-[CH₂NHCOCH₂]-, 4-[NHCOCH₂CH₂]-, a bond at position 4, 3-[CONH]-, 3-[CH₂O]-, 4-[CH₂SO₂NH]-, 3-[O]-, 3-[CH₂CONHNHCO]-, 3-[CH₂CONH(CH₂)₂]-, 3-[CH₂CONHCH₂]-, 3-[CH₂CO₂(CH₂)₂SO₂]-, 3-[SO₂]-, 3-[CH₂SO₂NH]-, or 4-[CH₂SO₂NH]-. The position of the linking moiety Q is defined with respect to the atom numbering depicted in formula (IA).
- 20 Suitably, Q represents 4-[S]-.
- Suitably, R¹² represents hydrogen, 4-CH₂CO₂H, 4-CH₂CH₂CO₂H, 4-CH₂OH, 3-NMe₂, 4-NH₂, 4-NMe₂, (3-Cl-4-morpholin-4-yl), 4-CH₂CN, 4-OCH₂-(1-Me-piperidin-4-yl), 3-CH₂CO₂H, 3-CONHMe, 3-CO₂H, 2-OH, 2-CO₂H, 3-CONH₂, 4-CONHMe, 3-[CONH(CH₂)₂OMe], 4-CO₂H, 4-CONH₂, 3-[CH₂CONH(CH₂)₂morpholin-4-yl], 4-Me, 3-CH₂CONH₂, 3-CH₂CONHOH, 2-CH₂CO₂Me, 2-CONHMe, 3-CH₂CONHMe, 2-CONH₂, 4-Ph, 4-CH₂CH₂OH, 4-morpholin-4-yl, 4-piperidin-1-yl, 4-CH₂NHCOMe, 3-NH₂, 4-NHCOMe, 3-NHCOMe, 4-N(Me)COMe, 4-CH₂NHCOMe, 4-Cl, 3-NHCONH₂, 4-CH₂NHCOMe, 4-CH₂CH₂NMe₂, 4-SO₂NH₂, 3-CH₂OH, or 4-NHSO₂Me.
- 25 Suitably, R¹² represents 3-CH₂CO₂H.
- Preferably, a compound of formula (IA) is Example A1 of Table A.
- It is considered that the compounds of formula (IA) are novel. Accordingly, the
- 30 present invention also provides a compound of formula (IA) or a derivative thereof.
- 35 There is a subgroup of compounds falling wholly within formula (I') being of formula (IB)



wherein;

- R^{10'} represents hydrogen or one or more substituents, suitably up to five, selected
5 from the list consisting of cyano, halo, carboxy, and hydroxyC₁-6alkyl;
R¹³ represents hydrogen;

- W represents -[S-CH=N]-, -[(CH₂)₂-4N(SO₂C₁-6alkyl)]-, -[(CH₂)₃-5]-, -
[N=C(C₁-6alkyl)-S]-, -[S-C(C₁-6alkyl)=N]-, -[O-C(C₁-6alkyl)=N]-, -[N=C(C₁-6alkyl)-
O]-, -[O-CH=N]-, -[CH=CH-N(C₁-6alkyl)]-, -[O-CO-NH]-, -[S-C(S(CH₂)₁-6CO₂C₁-
10 6alkyl)=N]-, -[S-C(S(CH₂)₁-6CO₂H)=N]-, -[CH=CH-CH=N]-, -[S-CO-NH]-, -[N(C₁-
6alkyl)-CH=N], -[S-C(halo)=N], -[S-C(SC₁-6alkyl)=N], -[NHCONH], -[S-C(Ph)=N], -
[S-C(NHC₁-6alkyl)=N], -[S-C(N(C₁-6alkyl)₂)=N], -[S-C(=O)N((CH₂)₁-6CO₂C₁-
6alkyl)], -[S-C(=O)N((CH₂)₁-6CO₂H)], -[CH=CH-S], -[S(CH₂)₁-6CO₂H]=N], -[S-
C(NHPh)=N], -[N(C₁-6alkyl)CON(C₁-6alkyl)], -[S-CO-N(C₁-6alkyl)], -[S-C((CH₂)₁-
15 6CO₂C₁-6alkyl)=N], -[S-C[(CH₂)₁-6CO₂H]=N], -[CH=C(CO₂H)-O], -[S-
C[NH(CH₂)₁-6N(C₁-6alkyl)₂]=N], -[S-CO-N[(CH₂)₁-6N(C₁-6alkyl)₂]], -[S-
C(Morpholin-4-yl)=N], -[S-CO-N(unsubstituted or substituted Ph)], -[S-CO-N((CH₂)₁-
6Ph)], -[CH=C(CO₂H)-N(C₁-6alkyl)], -[(CH₂)₂-4N(CO₂C₁-6alkyl)], -[(CH₂)₂-4NH], -
[(CH₂)₁-3CONH], -[S-C(NHC₁-6alkyl)=N], -[S-C(NH₂)=N], [NH-CO-O], -
20 [CH=C(CONH₂)-N(C₁-6alkyl)], -[O(CH₂)₁-2CONH], or -[S-C(NHCOC₁-6alkyl)=N].

Suitably, R^{10'} represents hydrogen, 3-CN, 2,3-di-F, 2,3,6-tri-F, 3-CO₂H, 2-F-3-Cl, 2-Cl-3-F, or 3-CH₂OH.

Favourably, R^{10'} represents 2,3-di-F.

Suitably, R¹³ represents hydrogen.

- 25 Suitably, W represents 3,4-[S-CH=N]-, 3,4-[CH₂CH₂N(SO₂Me)]-, 3,4-[
CH₂CH₂CH₂]-, 3,4-[N=C(Me)-S]-, 3,4-[S-C(Me)=N]-, 3,4-[O-C(Me)=N]-, 3,4-[
N=C(Me)-O]-, 3,4-[O-CH=N]-, 3,4-[CH=CH-N(Me)]-, 3,4-[O-C(O)-NH]-, 3,4-[S-
C(SCH₂CO₂Me)=N]-, 3,4-[S-C(SCH₂CO₂H)=N]-, 3,4-[CH=CH-CH=N]-, 3,4-[S-C(O)-
NH]-, 3,4-[N(Me)-CH=N], 3,4-[S-C(Cl)=N], 3,4-[S-C(SMe)=N], 3,4-[NHCONH], 3,4-[
30 S-C(Ph)=N], 3,4-[S-C(NHMe)=N], 3,4-[S-C(NMe₂)=N], 3,4-[S-
C(=O)N(CH₂CO₂Me)], 3,4-[S-C(=O)N(CH₂CO₂H)], 3,4-[CH=CH-S], 3,4-[S-
C[S(CH₂)₃CO₂H]=N], 3,4-[S-C(NHPh)=N], 3,4-[N(Me)CON(Me)], 3,4-[S-CO-N(Me)],
3,4-[S-C[(CH₂)₄CO₂Me]=N], 3,4-[S-C[(CH₂)₄CO₂H]=N], 3,4-[CH=C(CO₂H)-O], 3,4-[
35 S-C[NH(CH₂)₃NMe₂]=N], 3,4-[S-CO-N[(CH₂)₃NMe₂]], 3,4-[S-C(Morpholin-4-
yI)=N], 3,4-[S-CO-N(3-F-Ph)], 3,4-[S-CO-N(4-OMe-Ph)], 3,4-[S-CO-N(CH₂Ph)], 3,4-[
S-CO-N(3-NHCOMe-Ph)], 3,4-[CH=C(CO₂H)-N(Me)], 3,4-[CH₂CH₂N(CO₂t-Bu)],
3,4-[CH₂CH₂NH], 3,4-[CH₂CONH], 3,4-[S-C(NHEt)=N], 3,4-[S-C(NH₂)=N]-, 3,4-[S-

$\text{C}(\text{NHPr})=\text{N}$], 3,4-[$\text{NH}-\text{CO}-\text{O}$], 3,4-[$\text{CH}=\text{C}(\text{CONH}_2)-\text{N}(\text{Me})$], 3,4-[OCH_2CONH], or 3,4-[$\text{S}-\text{C}(\text{NHCOMe})=\text{N}$].

Favourably, W represents 3,4-[$\text{S}-\text{C}(\text{NH}_2)=\text{N}$]-.

Favourably, W represents 3,4-[CH_2CONH]-.

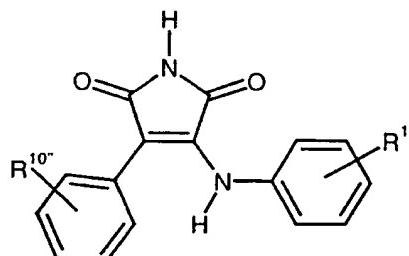
5 Favourably, W represents 3,4-[$\text{O}-\text{C}(\text{O})-\text{NH}$]-.

Favourably, W represents 3,4-[$\text{S}-\text{C}(\text{O})-\text{NH}$]-.

Preferably, a compound of formula (IB) is selected from the list consisting of Examples B10, B16, B47, and B49 of Table B.

10 It is considered that the compounds of formula (IB) are novel. Accordingly, the present invention also provides a compound of formula (IB) or a derivative thereof.

There is a subgroup of compounds falling wholly within formula (I) being of formula (IC)



(IC)

15

wherein;

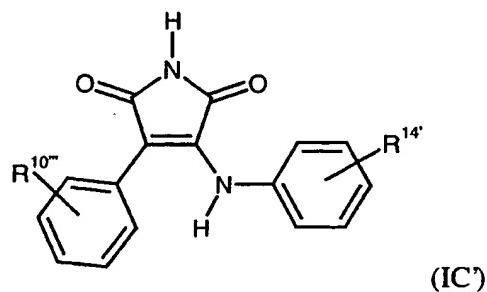
R^{10} " represents hydrogen or one or more, suitably up to five, substituents selected from the list consisting of halo, C_{1-6} alkyl, cyano, carboxy, nitro, C_{1-6} alkylcarbonylamino, and hydroxy C_{1-6} alkyl;

20 R^{14} represents hydrogen or one or more, suitably up to five, substituents selected from the list consisting of carboxycarbonylamino, unsubstituted or substituted C_{1-6} alkyl, halo, C_{1-6} alkylaminocarbonyl, C_{1-6} alkylamino, morpholinyl, C_{1-6} alkoxy C_{1-6} alkylaminosulphonyl, C_{1-6} alkylaminosulphonyl, C_{1-6} alkylcarbonyl, C_{1-6} alkylcarbonylamino, (perfluoro C_{1-6} alkyl)carbonylamino, C_{1-6} alkylthio, amino, nitro,

25 perfluoro C_{1-6} alkyl, aminocarbonyl C_{2-6} alkenyl, C_{1-6} alkoxy C_{1-6} alkylcarbonylamino, C_{1-6} alkylcarbonylamino C_{1-6} alkylcarbonylamino, hydroxy C_{1-6} alkylcarbonylamino, C_{1-6} alkoxycarbonyl C_{1-6} alkylcarbonylamino, carboxy C_{1-6} alkylcarbonylamino, hydroxy C_{1-6} alkylcarbonylamino, hydroxy, aminosulphonyl, carboxy C_{2-6} alkenyl, aminocarbonyl C_{1-6} alkylcarbonylamino, carboxy C_{1-6} alkyl, thiazolidindionyl C_{1-6} alkyl, C_{1-6} alkylcarbonylamino C_{1-6} alkyl, C_{1-6} alkylsulphonylamino C_{1-6} alkyl, (C_{1-6} alkoxy)hydroxyphosphinyl C_{1-6} alkyl, aminosulphonyl C_{1-6} alkyl, C_{1-6} alkoxyaminocarbonyl C_{1-6} alkyl, hydroxyaminocarbonyl C_{1-6} alkyl, C_{1-6} alkoxyaminocarbonyl C_{2-6} alkenyl, amino C_{1-6} alkyl, and C_{1-6} alkylaminocarbonyl C_{1-6} alkoxy.

30 35 Suitable substituents for C_{1-6} alkyl include C_{1-6} alkylcarbonylhydrazocarbonyl, thiazolidindionyl, (piperazinyl)carbonyl wherein the piperazinyl moiety may be unsubstituted or substituted, (morpholinyl)carbonyl, (piperidinyl)carbonyl, hydroxy C_{1-6} alkoxy.

- 6alkylaminocarbonyl, (di-C₁-6alkylamino)carbonyl, carboxy, C₁-6alkylaminosulphonyl, aminocarbonyl, (di-C₁-6alkylamino)C₁-6alkylaminocarbonyl, C₁-6alkoxycarbonylamino, C₁-6alkylcarbonylamino, C₁-6alkoxyC₁-6alkylcarbonylamino, C₁-6alkylcarbonylaminoC₁-6alkylcarbonylamino, hydroxyC₁-6alkylcarbonylamino, C₁-6alkoxycarbonylC₁-6alkylcarbonylamino, C₁-6alkoxyC₁-6alkylcarbonylamino, hydroxyC₁-6alkylcarbonylamino, C₁-6alkylaminosulphonyl, and (di-C₁-6alkylamino)sulphonyl.
- Suitable substituents for piperazinyl include C₁-6alkyl.
- Suitably, R^{10"} represents hydrogen, 2-F-3-Cl, 2-Cl-3-F, 4-NO₂, 4-I, 2-Cl, 4-NHCOMe, 2,3,5-tri-F, 3,5-di-Me, 2,3,6-tri-F, 2,3-di-F, 3-CN, 3-F, 2-Cl-5-F, 3-CO₂H, or 3-CH₂OH.
- Suitably, R¹⁴ represents hydrogen, 3-[CH₂-(1,3-thiazolidine-2,4-dion-5-yl)], 3,5-di-F, 3-Cl, 3-OCH₂CO₂H, 3-CONHMe-4-NHMe, 4-[CH₂CO(4-Me-piperazin-1-yl)], 2-(morpholin-4-yl), 3-[CH₂CO(morpholin-4-yl)], 3-[CH₂CO(piperidin-1-yl)], 4-[CH₂CO(piperidin-1-yl)], 4-[CH₂CONH(CH₂)₂OH], 4-[CH₂CONMe₂], 3-CONHMe-4-Cl, 3-SO₂NH(CH₂)₂OMe, 3-SO₂NH_nBu, 3-COME, 3-CH₂CO₂H, 3-NHCOMe, 4-NHCOCF₃, 2-Me, 2-Me-4-F, 2-Me-5-F, 3-Me, 2-SMe, 3-CF₃-4-NH₂, 3-CF₃-4-NHCOMe, 4-CH₂SO₂NHMe, 4-CH₂CH₂CONH₂, 4-Me, 3-[CH₂CONH(CH₂)₂NMe₂], 4-NH₂, 3-NO₂, 3-Cl, 3-NH₂, 2,3,4-tri-F, 3-F-5-CF₃, 4-O(CH₂)₃CO₂H, 4-CH₂NHCO₂tBu, 4-trans-CH=CHCONH₂, 4-NHCOCH₂OMe, 4-NHCOCH₂NHCOMe, 4-CH₂NHCOOnPr, 4-NHCOCH₂OH, 3-NHCOCH₂OMe, 4-NHCOCH₂CO₂tBu, 3-NHCOCH₂NHCOMe, 4-NHCOOnPr, 4-NHCOCH₂CO₂H, 4-CH₂NHCOCH₂OMe, 4-CH₂NHCOCH₂NHCOMe, 4-(CH₂)₃CO₂H, 4-(CH₂)₃CO₂H, 3-CH₂NHCO₂tBu, 4-CH₂NHCOCH₂OH, 4-NHCOMe, 3-NHCOCH₂OH, 3-OH-4-NHCOMe, 4-CH₂NHCOCH₂CO₂tBu, 3-CH₂CONH₂, 3-SO₂NH₂, 3-CH₂NHCOCH₂OMe, 3-CH₂NHCOCH₂NHCOMe, 3-CH₂NHCOCH₂OH, 4-trans-CH=CHCO₂H, 4-NHCO(CH₂)₂CONH₂, 4-O(CH₂)₃CONHMe, 4-CH₂SO₂NMe₂, 4-[CH₂-(1,3-thiazolidine-2,4-dion-5-yl)], 3-CH₂CH₂CO₂H, 4-CH₂CH₂CH₂CO₂H, 4-OH, 3,5-di-Cl-4-OH, 4-(CH₂)₂CO₂H, 3-F-4-OCH₂CO₂H, 4-NHCOCO₂H, 3-Me-4-trans-CH=CHCO₂H, 3-CH₂CONHNHCOMe, 4-(CH₂)₄NHCOMe, 4-(CH₂)₄NHSO₂Me, 3-CH₂NHSO₂Me, 4-CH₂CH₂P(O)(OEt)OH, 4-CH₂CH₂SO₂NH₂, 3-CH₂SO₂NH₂, 3-CH₂CONHOMe, 3-CH₂CONHOH, 4-trans-CH=CHCONHOMe, 4-CH₂NH₂, or 3-CH₂NH₂.
- There is a sub-group of compounds falling wholly within formula (I') and being of formula (IC')



wherein;

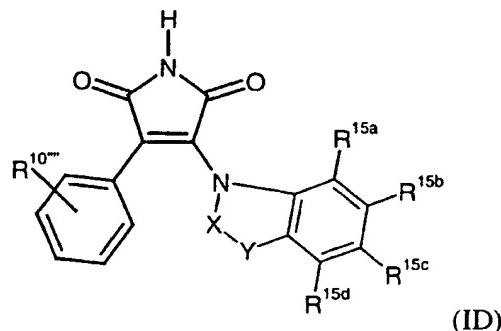
$R^{10''}$ and $R^{14'}$ are as defined for $R^{10''}$ and R^{14} respectively in formula (IC), with the proviso that formula (IC') does not include

- 5 3-phenylamino-4-phenyl-1H-pyrrole-2,5-dione.

It is considered that compounds of formula (IC') are novel. Accordingly, the present invention also provides a compound of formula (IC') or a derivative thereof.

There is a subgroup of compounds falling wholly within formula (I') being of formula (ID)

10



wherein;

- 15 $R^{10'''}$ represents hydrogen or one or more, suitably up to five, substituents selected from the list consisting of halo and C_{1-6} alkyl;

$X-Y$ represents $-[CH((CH_2)_{1-6}OH)-(CH_2)_{1-4}]$, $-[CH_2]_{1-4}$, or $-[CH((CH_2)_{1-6}(OC_{1-6}alkyl))-(CH_2)_{1-4}]$;

R^{15a} represents hydrogen;

R^{15b} represents hydrogen;

20 R^{15c} represents hydrogen;

R^{15d} represents hydrogen.

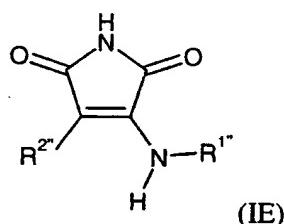
Suitably, $R^{10'''}$ represents hydrogen, 2,3-di-F, 2,3,6-tri-F, 3,5-di-Me, or 2-Cl.

Suitably, $X-Y$ represents $-[CH(CH_2OH)CH_2]$, $-[(CH_2)_2]$, $-[(CH_2)_3]$, or $-[CH(CH_2OMe)CH_2]$.

- 25 It is considered that compounds of formula (ID) are novel. Accordingly, the present invention also provides a compound of formula (ID) or a derivative thereof.

There is a subgroup of compounds falling wholly within formula (I') being of formula (IE)

30



wherein;

R¹" is substituted pyridinyl;

R²" is substituted phenyl;

Suitable substituents for pyridinyl include aryloxy, C₁-6alkyl, cyanoC₁-6alkyl, carboxyC₁-6alkyl, or C₁-6alkoxycarbonyl.

Suitable substituents for phenyl include halo.

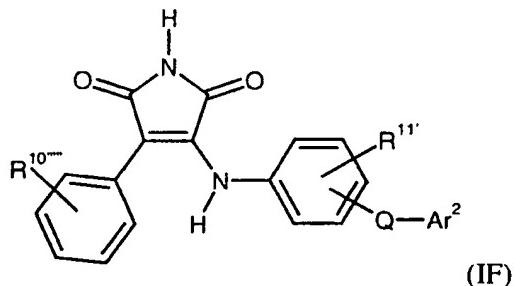
Suitably, R¹" is 2-[(CH₂)₃CN]-3-Me-pyridin-5-yl, 2-Me-pyridin-3-yl, 2-[(CH₂)₂CO₂H]-pyridin-5-yl, 2-[(CH₂)₃CN]-3-(CO₂Et)-pyridin-5-yl, 2-[(CH₂)₄CO₂H]-pyridin-5-yl, 2-OPh-pyridin-5-yl, or 2-[(CH₂)₃CN]-pyridin-3-yl.

Suitably, R²" is 2,3-difluorophenyl.

It is considered that compounds of formula (IE) are novel. Accordingly, the present invention also provides a compound of formula (IE) or a derivative thereof.

There is a subgroup of compounds falling wholly within formula (I) being of formula (IF)

15



wherein;

R¹⁰"" represents hydrogen or one or more, suitably up to five, substituents selected from the list consisting of halo;

R¹¹' represents hydrogen or hydroxy;

Q represents a bond, -[O]-, -[(CH₂)₁₋₆CONH]-, -[(CH₂)₁₋₆CO₂(CH₂)₁₋₆]-, -[O(CH₂)₁₋₆N(C₁₋₆alkyl)]-, -[O(CH₂)₁₋₆]-, -[S(CH₂)₁₋₆]-, -[(CH₂)₁₋₆SO₂NH]-, or -[NHCO(CH₂)₁₋₆]-;

Ar² represents oxazolyl, benzothiazolyl, quinolinyl, oxadiazolyl, pyrimidinyl, pyrazinyl, dihydropyridazinonyl, pyrazolyl, imidazolyl, pyrazinonyl, dihydro-oxadiazinonyl, pyridazinonyl, and pyridinyl.

Suitable substituents for oxazolyl include C₁-6alkyl.

Suitable substituents for benzothiazolyl include C₁-6alkyl.

Suitable substituents for oxadiazolyl include C₁-6alkyl.

Suitable substituents for pyrimidinyl include hydroxy.

Suitable substituents for dihydropyridazinonyl include C₁-6alkyl.

Suitable substituents for pyrazinyl include C₁-6alkoxy.

Suitable substituents for pyridinyl include C₁-6alkyl, C₁-6alkoxy, and amino.

Suitably, R¹⁰"" represents 2,3-di-F.

Suitably, Q represents a bond at position 3, 4-[NHCO(CH₂)₂]-, 4-[O], 3-[bond], 3-[CH₂CONH], 3-[CH₂CO₂CH₂], 4-[O(CH₂)₂NMe], 4-[OCH₂], 4-[SCH₂], 3-

[CH₂SO₂NH], or a bond at position 4. The position of the linking moiety Q is defined with respect to the atom numbering depicted in formula (IF).

- Suitably, Ar² represents 5-oxazolyl, 3-pyridinyl, 5-Me-2-oxazolyl, 2-Me-4-oxazolyl, 6-Me-benzothiazol-2-yl, 3-pyridinyl, benzothiazol-2-yl, quinolin-3-yl, 3-Me-5, 1,2,4-oxadiazol-5-yl, 2-Me-pyridin-3-yl, 5-Me-pyridin-3-yl, 2-OMe-pyridin-5-yl, 3-NH₂-pyridin-2-yl, pyridin-2-yl, pyrimidin-4-yl, pyrazin-2-yl, 2-OH-pyrimidin-5-yl, 5-Me-4,5-dihydro-2H-pyridazin-3-on-6-yl, 2,5-di-Me-4,5-dihydro-2H-pyridazin-3-on-6-yl, 1H-pyrazol-3-yl, 1H-imidazol-4-yl, 2-OMe-pyrazin-5-yl, 1H-pyrazin-2-on-5-yl, 5,6-dihydro-4H-[1,3,4]-oxadiazin-5-on-2-yl], 4,5-dihydro-2H-pyridazin-3-on-6-yl, or 2H-pyridazin-3-on-6-yl.

It is considered that compounds of formula (IF) are novel. Accordingly, the present invention also provides a compound of formula (IF) or a derivative thereof.

- Certain of the compounds of formula (I) may contain chiral atoms and/or multiple bonds, and hence may exist in one or more stereoisomeric forms. The present invention encompasses all of the isomeric forms of the compounds of formula (I) whether as individual isomers or as mixtures of isomers, including geometric isomers, tautomers, and racemic modifications.

Alkyl groups referred to herein, including those forming part of other groups, include straight or branched chain alkyl groups containing up to twelve, suitably up to six carbon atoms. These alkyl groups may be optionally substituted with up to five, suitably up to three, groups selected from the list consisting of aryl, heterocyclyl, alkylthio, alkenylthio, alkynylthio, arylthio, heterocyclylthio, alkoxy, arylalkoxy, arylalkylthio, amino, mono- or di-alkylamino, cycloalkyl, cycloalkenyl, carboxy and esters thereof, phosphonic acid and esters thereof, mono- or dialkylaminosulphonyl, aminosulphonyl, cyano, alkylcarbonylamino, arylcarbonylamino, arylaminocarbonyl, arylalkylaminocarbonyl, arylalkylcarbonylamino, thiazolidinedionyl, piperazinylcarbonyl wherein the piperazine may be unsubstituted or substituted, morpholinylcarbonyl, piperidinylcarbonyl, hydroxyalkylaminocarbonyl, dialkylaminocarbonyl, aminocarbonyl, dialkylaminoalkylaminocarbonyl, alkoxy carbonylamino, alkoxyalkylcarbonylamino, alkylcarbonylaminoalkylcarbonylamino, alkoxy carbonylalkylcarbonylamino, alkylaminocarbonyl, aminosulphonyl, arylsulphonylamino, alkylsulphonylamino, hydroxy, morpholinylalkylaminocarbonyl, hydroxyaminocarbonyl, and halogen.

Alkenyl and alkynyl groups referred to herein include straight and branched chain groups containing from two to twelve, suitably from two to six, carbon atoms. These alkenyl and alkynyl groups may be optionally substituted with up to five, suitably up to three, groups including those substituents described hereinbefore for the alkyl groups.

As used herein the term "carbocyclic" includes aromatic carbocyclic rings, for example aryl groups, and non-aromatic carbocyclic groups, for example cycloalkyl and cycloalkenyl groups, and fused carbocyclic ring systems wherein the carbocyclic rings may be aromatic or non-aromatic, for example indanyl.

Cycloalkyl and cycloalkenyl groups referred to herein include groups having between three and eight ring carbon atoms. These cycloalkyl and cycloalkenyl groups may be optionally substituted with up to five, suitably up to three, groups including those substituents hereinbefore described for the alkyl groups.

As used herein, the term "aryl" includes phenyl, naphthyl, and biphenyl groups, especially phenyl.

- Suitably optional substituents for any aryl group include up to five substituents selected from the list consisting of alkylbenzothiazolyl, pyridinyloxy, benzothiazolyl,
 5 quinolinylaminocarbonylalkyl, alkyloxadiazolyl, (alkyl)pyridinylaminocarbonylalkyl, (alkoxy)pyridinylaminocarbonylalkyl, pyridinylaminocarbonylalkyl, (amino)pyridinylalkoxycarbonylalkyl, (pyridinyl)(alkyl)aminoalkoxy, pyridinylalkoxy, pyrimidinylaminocarbonylalkyl, pyrazinylaminocarbonylalkyl, hydroxypyrimidinyl, mono or dialkyldihydro-2H-pyridazinonyl, 1H-pyrazolyl, 1H-imidazolylalkylthio,
 10 pyridinylaminosulphonylalkyl, alkoxyprazinyl, pyrazinonyl, dihydro-4H-oxadiazinonyl, dihydro-2H-pyridazinonyl, 2H-pyridazinonyl, aryl, hydroxyalkyl, morpholinyl, piperidinyl, cyanoalkyl, (alkylpiperidinyl)alkoxy, (alkylcarbonyl)(alkyl)amino, alkylcarbonylaminoalkyl, (dialkyl)aminoalkyl, aminosulphonyl, alkylsulphonylamino, carboxyalkyl, carboxyalkoxy, (thiazolidindionyl)alkyl, alperhaloalkyl,
 15 arylaminocarbonyl, aralkyaminocarbonyl, hydroxyalkylaminocarbonyl, arylamino, aminosulphonyl, alkylsulphonylamino, mono- and di-alkylamino, mono- and di-alkylaminocarbonyl, arylaminocarbonylalkyl, arylcarbonyl, aralkoxy, arylcarbonylamino, alkoxyalkylaminocarbonyl, aralkylcarbonylamino, aralkylcarbonylaminoalkyl, aminocarbonyl, morpholinylalkylaminocarbonylalkyl, arylaminosulphonyl,
 20 arylcarbonylaminoalkyl, arylsulphonylamino, aminocarbonylalkyl, hydroxyaminocarbonylalkyl, aryl, alkylaminocarbonyl, thiazolidinedionylalkyl, carboxyalkoxy, (alkylpiperazinyl)carbonylalkyl, morpholinyl, morpholinylcarbonylalkyl, piperidinylcarbonylalkyl, hydroxyalkylaminocarbonylalkyl, mono- and di-alkylaminocarbonylalkyl, alkoxyalkylaminosulphonyl, alkoxyamino,
 25 perhaloalkylcarbonylamino, alkylaminosulphonylalkyl, mono- and di-alkylaminoalkylaminocarbonylalkyl, carboxyalkoxy, alkoxy carbonylaminoalkyl, aminocarbonylalkenyl, alkoxyalkylcarbonylamino, alkylcarbonylaminoalkylcarbonyl, hydroxyalkylcarbonylamino, alkoxy carbonylalkylcarbonylaminocarbonyl,
 30 carboxyalkylcarbonylamino, alkoxyalkylcarbonylaminoalkyl, alkylcarbonylaminoalkylcarbonylaminocarbonyl, hydroxyalkylcarbonylaminoalkyl, carboxyalkenyl, aminocarbonylalkylcarbonylamino, alkylaminocarbonylalkoxy, alkylaminosulphonylalkyl, aminocarbonylalkyl, oxazolyl, pyridinylalkylcarbonylamino, alkyloxazolyl, alkylthio, alkylaminocarbonylalkyl, halo, alkyl, alkenyl, substituted
 35 alkenyl, arylalkyl, alkoxy, alkoxyalkyl, haloalkyl, haloalkyloxy, hydroxy, hydroxyalkyl, nitro, amino, cyano, cyanoalkyl, mono- and di-N-alkylamino, acyl, acylamino, N-alkylacylamino, acyloxy, carboxy, carboxyalkyl, carboxyalkylcarbonyl, carboxyalkenyl, ketoalkylester, carbamoyl, carbamoylalkyl, mono- and di-N-alkylcarbamoyl, alkoxy carbonyl, alkoxy carbonylalkyl, aryloxy, arylthio, aralkyloxy, aryloxycarbonyl,
 40 ureido, guanidino, morpholino, adamantyl, oxazolyl, aminosulphonyl, alkylaminosulphonyl, alkylthio, haloalkylthio, alkylsulphinyl, alkylsulphonyl, cycloalkyl, heterocyclyl, heterocyclalkyl, alkoxy carbonyl, trityl, substituted trityl, mono- or bis-alkylphosphonate or mono- or bis-alkylphosphonateC₁₋₆alkyl or any two adjacent

substituents on the phenyl ring together with the carbon atoms to which they are attached form a carbocyclic ring or a heterocyclic ring.

- As used herein the terms "heterocyclyl" and "heterocyclic" suitably include, unless otherwise defined, aromatic and non-aromatic, single and fused, rings suitably containing up to four heteroatoms in each ring, each of which is selected from oxygen, nitrogen and sulphur. Each ring suitably has from 4 to 7, preferably 5 or 6, ring atoms. These heterocyclyl and heterocyclic rings may be unsubstituted or substituted by up to five substituents. A fused heterocyclic ring system may include carbocyclic rings and need include only one heterocyclic ring. Examples of heterocyclyl and heterocyclic rings include pyridyl, indolinyl, quinolinyl, indolyl, benzoxazolyl, benzothiazolyl, benzothiazolinonyl, benzimidazolinonyl, benzothiophenyl, benzofuranyl, indolinonyl, benzoxazinonyl, quinolinyl, oxadiazolyl, pyrimidinyl, pyrazinyl, dihydropyridazinonyl, pyrazolyl, imidazolyl, pyrazinonyl, dihydro-oxadiazinonyl, pyridazinonyl, benzoxazolinonyl, is benzimidazolyl, benzimidazolinonyl, benzothiophenyl, benzofuranyl, indolinonyl, 2H-benzothiazin-3(4H)-onyl, and benzoxazolinonyl.

- Substituents for any heterocyclyl or heterocyclic group are suitably selected from aryloxy, cyano, carboxyalkoxy, morpholinyl, hydroxyalkylaminocarbonyl, alkoxyalkylaminosulphonyl, alkylaminosulphonyl, arylcarbonylamino, aralkylcarbonylamino, aralkenylcarbonylamino, perhalocarbonylamino, perhaloalkyl, aminocarbonyl, nitro, aminocarbonylalkenyl, alkoxyalkylcarbonylamino, alkylcarbonylaminoalkylcarbonylamino, hydroxyalkylcarbonylamino, carboxyalkenyl, aminocarbonylalkylcarbonylamino, alkylaminocarbonylalkoxy, aryl, arylcarbonyl, alkylenedioxy, aryloxy, aralkyloxy, perhaloalkylthio, alkylcarbonyl, alkoxy carbonylalkylthio, carboxyalkylthio, hydroxyalkyl, alkoxyalkyl, cyanoalkyl, carboxyalkyl, alkoxy carbonyl, halogen, alkyl, arylalkyl, alkoxy, alkoxyalkyl, haloalkyl, hydroxy, amino, mono- and di-N-alkylamino, acylamino, carboxy and salts and esters thereof, carbamoyl, mono- and di-N-alkylaminocarbonyl, aryloxycarbonyl, alkoxy carbonylalkyl, aryl, oxy groups, ureido, guanidino, sulphonylamino, aminosulphonyl, alkylthio, alkylsulphinyl, alkylsulphonyl, heterocyclyl and heterocyclylalkyl.

As used herein the terms "halogen" or 'halo' include iodo, bromo, chloro or fluoro, especially chloro or fluoro.

- Suitable derivatives of the compounds of the invention are pharmaceutically acceptable derivatives.

35 Suitable derivatives of the compounds of the invention include salts and solvates.

Suitable pharmaceutically acceptable derivatives include pharmaceutically acceptable salts and pharmaceutically acceptable solvates.

- 40 Suitable pharmaceutically acceptable salts include metal salts, such as for example aluminium, alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxy alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)amine or tri-(2-hydroxyethyl)amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, N,N'-

bisdehydroabietylamine, glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine, quinine or quinoline.

5 Suitable pharmaceutically acceptable salts also includes pharmaceutically acceptable acid addition salts, such as those provided by pharmaceutically acceptable inorganic acids or organic acids.

Suitable pharmaceutically acceptable acid addition salts provided by pharmaceutically acceptable inorganic acids includes the sulphate, nitrate, phosphate, borate, hydrochloride and hydrobromide and hydroiodide.

10 Suitable pharmaceutically acceptable acid addition salts provided by pharmaceutically acceptable organic acids includes the acetate, tartrate, maleate, fumarate, malonate, citrate, succinate, lactate, oxalate, benzoate, ascorbate, methanesulphonate, α -keto glutarate and α -glycerophosphate.

Suitable pharmaceutically acceptable solvates include hydrates.

15 For the avoidance of doubt when used herein the term "diabetes" includes diabetes mellitus, especially Type 2 diabetes, and conditions associated with diabetes mellitus.

The term 'conditions associated with diabetes' includes those conditions associated with the pre-diabetic state, conditions associated with diabetes mellitus itself and complications associated with diabetes mellitus.

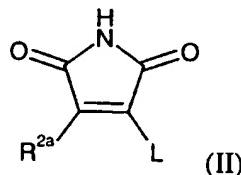
20 The term 'conditions associated with the pre-diabetic state' includes conditions such as insulin resistance, impaired glucose tolerance and hyperinsulinaemia.

25 The term 'conditions associated with diabetes mellitus itself' include hyperglycaemia, insulin resistance and obesity. Further conditions associated with diabetes mellitus itself include hypertension and cardiovascular disease, especially atherosclerosis and conditions associated with insulin resistance. Conditions associated with insulin resistance include polycystic ovarian syndrome and steroid induced insulin resistance.

30 The term 'complications associated with diabetes mellitus' includes renal disease, especially renal disease associated with Type II diabetes, neuropathy and retinopathy. Renal diseases associated with Type II diabetes include nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

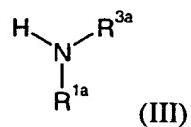
A further aspect of the invention provides a process for the preparation of a compound of formula (I'), which process comprises reaction of a compound of formula (II)

35



wherein;

40 R^{2a} is as defined for R² in formula (I) and L is a leaving group, with a compound of formula (III)



wherein;

- 5 R^{1a} and R^{3a} are as defined for R^1 and R^3 respectively in formula (I), and thereafter, if required, carrying out one or more of the following optional steps:
- (i) converting a compound of formula (I') to a further compound of formula (I');
 - (ii) removing any necessary protecting group;
 - (iii) preparing an appropriate derivative of the compound so formed.
- 10 Examples of suitable leaving groups, L, are chloro, bromo, triflate, and hydroxy. The reaction between the compounds of formulae (II) and (III) is carried out in any suitable solvent, for example 1-methyl-2-pyrrolidinone, tetrahydrofuran, or methanol, under conventional amination conditions at any temperature providing a suitable rate of formation of the required product, generally an elevated temperature, over a suitable reaction time.
- 15 Suitable reaction temperatures include those in the range of 60°C to 220°C and, as appropriate, the reflux temperature of the solvent. When the compound of formula (III) is a weak nucleophile, then the reaction may be assisted by, for example, using temperatures at the upper end of this range, generating the anion of the compound of formula (III) *in situ* using, for example, sodium hydride, or by using a basic catalyst such as triethylamine. Conventional methods of heating also include the use of microwave heating devices, for example a microwave reactor, such as a 100 watt reactor.
- 20 The reaction products are isolated using conventional methods. Typically, the reaction mixture is cooled, the residue acidified and the products extracted using solvent extraction, suitably using an organic solvent.
- 25 The reaction products are purified by conventional methods, such as chromatography and trituration.
- 30 Crystalline product may be obtained by standard methods.
- 35 In a preferred aspect, a solution of the compound of formula (II) and a compound of formula (III) in methanol is heated to reflux from between 1 to 4 days, then cooled and concentrated. The residue is then acidified with hydrochloric acid, and extracted with ethyl acetate. The organic extracts are then washed with water, brine, dried with anhydrous magnesium sulphate, and the solvent is removed. The product is then purified by standard methods such as trituration or chromatography, on silica gel, to afford the desired compound.
- 40 In a further preferred aspect, a solution of the compound of formula (II) and a compound of formula (III) in 1-methyl-2-pyrrolidinone is heated at 69°C from between 1 to 4 days, then cooled and concentrated. The residue is then acidified with hydrochloric acid, and extracted with ethyl acetate. The organic extracts are then washed with water, brine, dried with anhydrous magnesium sulphate, and the solvent is removed. The

product is then purified by standard methods such as trituration or chromatography, on silica gel, to afford the desired compound.

The above mentioned conversion of a compound of formula (I') into another compound of formula (I) includes any conversion which may be effected using

5 conventional procedures, but in particular the said conversions include any combination of:

- (i) for a compound of formula (IA), converting one group R¹¹ into another group R¹¹;
- (ii) for a compound of formula (IA), converting one group R¹² into another group R¹², and;
- 10 (iii) for a compound of formula (IC'), converting one group R¹⁴ into another group R¹⁴.

The above mentioned conversions (i) to (iii) may be carried out using any appropriate method under conditions determined by the particular groups chosen.

15 For a compound of formula (IA);

suitable conversions of one group R¹¹ into another group R¹¹, as in conversion (i), include converting a group R¹¹ which represents carboxy into a group R¹¹ which represents alkylaminocarbonyl; such conversion may be carried out using a conventional procedure for the formation of amide bonds, for example treating an appropriately 20 protected compound of formula (I) with an amine in the presence of suitable activating agents such as a mixture of 1-hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide.

Suitable conversions of one group R¹² into another group R¹², as in conversion (ii), include:

25 (a). converting a group R¹² which contains a carboxy group into a group R¹² which contains an alkylaminocarbonyl group; such a conversion may be carried out using a conventional procedure for the formation of amide bonds, for example treating an appropriately protected compound of formula (I) with an amine in the presence of suitable activating agents such as a mixture of 1-hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide.

(b). converting a group R¹² which contains a carboxy group into a group R¹² which contains an aminocarbonyl group; such a conversion may be carried out using a conventional procedure for the formation of amide bonds, for example treating an appropriately protected compound of formula (I) with the ammonium salt of N-

30 hydroxysuccinimide in the presence of a suitable activating agent such as 1,3-dicyclohexylcarbodiimide.

(c). converting a group R¹² which contains a carboxy group into a group R¹² which contains a hydroxyaminocarbonyl group; such a conversion may be carried out using a conventional procedure for the formation of amide bonds, for example treating an

35 appropriately protected compound of formula (I) with O-(t-butyldimethylsilyl)hydroxylamine in the presence of suitable activating agents such as a mixture of 1-hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide.

For a compound of formula (IC');

- suitable conversions of one group R¹⁴ into another group R¹⁴, as in conversion (iii), include:
- (a). converting a group R¹⁴ which represents nitro into a group R¹⁴ which represents amino; such a conversion may be carried out using a conventional reduction procedure,
5 for example hydrogenating an appropriately protected compound of formula (I).
- (b). converting a group R¹⁴ which represents amino into a group R¹⁴ which represents acylamino; such a conversion may be carried out using a conventional procedure for the formation of amide bonds, for example treating an appropriately protected compound of formula (I) with a carboxylic acid in the presence of suitable activating agents such as a mixture of 1-hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide.
- 10 (c). converting a group R¹⁴ which represents aminoalkyl into a group R¹⁴ which represents acylaminoalkyl; such a conversion may be carried out using a conventional procedure for the formation of amide bonds, for example treating an appropriately protected compound of formula (I) with a carboxylic acid in the presence of suitable activating agents such as a mixture of 1-hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide.
- 15

The above mentioned conversions may as appropriate be carried out on any of the intermediate compounds mentioned herein.

Suitable protecting groups in any of the above mentioned reactions are those used conventionally in the art. The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected. Thus for example a benzyloxy group may be prepared by treatment of the appropriate compound with a benzyl halide, such as benzyl bromide, and thereafter, if required, the benzyl group may be conveniently removed using catalytic hydrogenation or a mild ether cleavage reagent such as trimethylsilyl iodide or boron tribromide.

Where appropriate individual isomeric forms of the compounds of formula (I) may be prepared as individual isomers using conventional procedures.

The absolute stereochemistry of compounds may be determined using conventional methods, such as X-ray crystallography.

30 The derivatives of the compounds of formula (I), including salts and/or solvates, may be prepared and isolated according to conventional procedures.

The compounds of formula (II) are known compounds or they may be prepared using methods analogous to those used to prepare compounds such as those described in International Patent Application, Publication Number WO97/34890 and Wiley, R.H. and Slaymaker, S.C. *J. Am. Chem. Soc.* (80) 1385 (1958). The compounds of formula (II) may be inter-converted in an analogous manner to the above mentioned inter-conversions of the compounds of formula (I).

40 The compounds of formula (III) are either commercially available, or are reported in the chemical literature, or are prepared by analogy with known conventional literature procedures, for example those disclosed in *J. Org. Chem.* 1998, 63, 6338, *Tet. Lett.* 1984, 25, 3383, *Synlett.* 1997, 133, *Synth. Commun.* 1995, 25, 1077, *Bioorg. Med. Chem. Lett.* 1997, 7, 1345, *Synthesis* 1994, 1413, and *Chem. Pharm. Bull.* 1982, 30, 3580, *J. Het. Chem.* 1992, 29, 1069, or in standard reference texts of synthetic methodology such as J. March, *Advanced Organic Chemistry*, 3rd Edition (1985), Wiley Interscience.

3-Phenylamino-4-phenyl-1H-pyrrole-2,5-dione may be prepared according to procedures disclosed in *J. Amer. Chem. Soc.* 1958, 80, 1385.

As stated above, the compounds of formula (I), or pharmaceutically acceptable derivatives thereof, are indicated to be useful as inhibitors of glycogen synthase kinase-3.

- 5 Thus the present invention further provides a compound of formula (I), or a pharmaceutically acceptable derivative thereof, for use as an inhibitor of glycogen synthase kinase-3, and especially for use in the treatment of conditions associated with a need for the inhibition of GSK-3, such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, 10 neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and manic depression, hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, inflammation and immunodeficiency.

- 15 The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable derivative thereof, for the manufacture of a medicament for the treatment of conditions associated with a need for the inhibition of GSK-3, such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and manic depression, hair loss, obesity, 20 atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, inflammation and immunodeficiency.

- 25 In a further aspect of this invention, there is provided a compound of formula (I), or a pharmaceutically acceptable derivative thereof, for use as an active therapeutic substance.

Preferably, the compounds of formula (I), or pharmaceutically acceptable derivatives thereof, are administered as pharmaceutically acceptable compositions.

- 30 Accordingly, the invention also provides a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier.

- 35 Neurotraumatic diseases include both open or penetrating head trauma, such as caused by surgery, or a closed head trauma injury, such as caused by an injury to the head region, ischaemic stroke including acute stroke, particularly to the brain area, transient ischaemic attacks following coronary by-pass and cognitive decline following other transient ischaemic conditions.

- 40 The active compounds are usually administered as the sole medicament agent but they may be administered in combination with other medicament agents as dictated by the severity and type of disease being treated. For example in the treatment of diabetes, especially Type 2 diabetes, a compound of formula (I), or a pharmaceutically acceptable derivative thereof, may be used in combination with other medicament agents, especially antidiabetic agents such as insulin secretagogues, especially sulphonylureas, insulin sensitizers, especially glitazone insulin sensitizers (for example thiazolidinediones), or with biguanides or alpha glucosidase inhibitors or the compound of formula (I), or a

pharmaceutically acceptable derivative thereof, may be administered in combination with insulin.

- 5 The said combination comprises co-administration of a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and an additional medicament agent or the sequential administration of a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and the additional medicament agent.

10 Co-administration includes administration of a pharmaceutical composition which contains both a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and the additional medicament agent or the essentially simultaneous administration of separate pharmaceutical compositions of a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and the additional medicament agent.

15 The compositions of the invention are preferably adapted for oral administration. However, they may be adapted for other modes of administration.

20 The compositions may be in the form of tablets, capsules, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations, such as oral or sterile parenteral solutions or suspensions. In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit dose.

25 Preferably the composition are in unit dosage form. A unit dose will generally contain from 0.1 to 1000 mg of the active compound.

30 Generally an effective administered amount of a compound of the invention will depend on the relative efficacy of the compound chosen, the severity of the disorder being treated and the weight of the sufferer. However, active compounds will typically be administered once or more times a day for example 2, 3 or 4 times daily, with typical total daily doses in the range of from 0.1 to 800 mg/kg/day.

35 Suitable dose forms for oral administration may be tablets and capsules and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulphate.

40 The solid oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

45 Oral liquid preparations may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil,

fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

- For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, a preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

- The formulations mentioned herein are carried out using standard methods such as those described or referred to in reference texts such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) or the above mentioned publications.

Suitable methods for preparing and suitable unit dosages for the additional medicament agent, such as the antidiabetic agent mentioned herein include those methods and dosages described or referred to in the above mentioned reference texts.

25

GSK-3 Assays

Types of GSK-3 assay used to test the compounds of the invention include the following:

- Type 1:** The GSK-3 specific peptide used in this assay was derived from the phosphorylation site of glycogen synthase and its sequence is:
- 30 YRRAAVPPSPSLRHSSPHQ(S)EDEEE. (S) is pre-phosphorylated as is glycogen synthase in vivo and the three consensus sites for GSK-3 specific phosphorylation are underlined. The buffer used to make up the glycogen synthase peptide and [γ -³³P] ATP consisted of MOPS 25mM, EDTA 0.2mM, MgAcetate 10mM, Tween-20 0.01% and mercaptoethanol 7.5mM at pH 7.00.
- 35 The compounds were dissolved in dimethyl sulphoxide (DMSO) to a final concentration of 100mM. Various concentrations were made up in DMSO and mixed with the substrate (GSK-3 peptide) solution (to a final concentration 20uM) described in the above section along with rabbit or human GSK-3 α and GSK-3 β (final concentration 0.5U/ml enzyme). The reactions were initiated with the addition of [γ -³³P] ATP (500cpm/pmole) spiked into
- 40 a mixture of ATP (final concentration of 10 μ M). After 30 min at room temperature the reaction was terminated by the addition of 10 μ l of H₃PO₄ / 0.01% Tween-20 (2.5%). A volume (10 μ l) of the mixture was spotted onto P-30 phosphocellulose paper (Wallac & Berthold, EG&G Instruments Ltd, Milton Keynes). The paper was washed four times in H₃PO₄ (0.5%), 2 mins for each wash, air dried and the radioactive phosphate

incorporated into the synthetic glycogen synthase peptide, which binds to the P-30 phosphocellulose paper, was counted in a Wallac microbeta scintillation counter.

Analysis of Data: Values for IC₅₀ for each inhibitor were calculated by fitting a four-parameter logistic curve to the model : cpm=lower+(upper-lower) /(1 + (concentration/IC₅₀)^{slope}).

- 5 **Type 2:** This protocol is based on the ability of the kinase to phosphorylate a biotinylated 26 mer peptide, Biot- KYRRAAVPPPSPLSRHSSPHQ(S)EDEEE, the sequence of which is derived from the phosphorylation site of glycogen synthase, where (S) is a pre-phosphorylated serine as in glycogen synthase *in vivo* and the three consensus 10 sites for GSK-3 specific phosphorylation are underlined. The phosphorylated biotinylated peptide is then captured onto Streptavidin coated SPA beads (Amersham Technology), where the signal from the ³³P is amplified via the scintillant contained in the beads.
- 15 Using microtitre plates, GSK-3 was assayed in 50 mM MOPS buffer, pH 7.0, containing 5% glycerol, 0.01% Tween-20, 7.5 mM 2-mercaptoethanol, 10 mM magnesium acetate, 8 uM of the above peptide, and 10 uM [³³P]-ATP. After incubation at room temperature, 20 the reaction was stopped by addition of 50 mM EDTA solution containing the Streptavidin coated SPA beads to give a final 0.2 mgs. Following centrifugation, the microtitre plates are counted in a Trilux 1450 microbeta liquid scintillation counter (Wallac). IC₅₀ values are generated for each compound by fitting to a four parameter model.

The most potent compounds of the present invention show IC₅₀ values in the range of 1 to 100 nM.

No adverse toxicological effects are expected for the compounds of the invention, when administered in accordance with the invention.

- 25 The following Syntheses illustrate the invention, but do not limit it in any way.

Synthesis 1

3-[4-[3-(Carboxymethyl)phenylthio]phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example A1)

- 30 A mixture of 3-(4-Aminophenylthio)phenylacetic acid (0.500 g, 1.93 mmol), 3-chloro-4-(4-chlorophenyl)-1H-pyrrole-2,5-dione (0.200 g, 0.80 mmol) and 1-methyl-2-pyrrolidinone (4.0 mL) was heated in a sealed tube in a hotblock set at 69°C for 28.5 hours. The mixture was diluted with aqueous hydrochloric acid (10 mL) and extracted with ethyl acetate (2x20 mL). The combined organics were washed with brine (2x10 mL), dried over anhydrous magnesium sulphate and evaporated to dryness. The residue was chromatographed on silica gel using a gradient of dichloromethane-methanol as eluent to give a solid.
- 35 ¹H NMR (DMSO-d₆): δ3.55 (2H, s), δ6.82 (3H, m), δ7.09 (8H, m), δ9.88 (1H, s), δ10.98 (1H, s), δ12.39 (1H, bs).

- 40 MS (APCI +ve): [M+H]⁺ at m/z 467 (C₂₄H₁₆F₂N₂O₄S requires [M+H]₊ at m/z 467.

Synthesis 2

3-[4-[3-(Methylaminocarbonylmethyl)phenylthio]phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example A2)

Methylamine (0.08mL, 2M in tetrahydrofuran, 0.17mmol) was added to a solution of 3-[4-[3-(carboxymethyl)phenylthio]phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Table A, Example A1; 0.070 g, 0.16 mmol), 1-hydroxybenzotriazole (0.022 g, 0.17 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.031 g, 0.17 mmol in dichloromethane (2.5 mL). The mixture was stirred at ambient temperature for 18h. Saturated aqueous sodium bicarbonate (5 mL) was added, stirring continued for 5 minutes and the organic layer transferred directly onto a column of silica gel. Elution with dichloromethane-methanol gave the product as a solid.

¹H NMR (DMSO-d₆): δ2.54 (3H, d), δ3.36 (2H, s), δ6.80 (3H, m), δ7.14 (8H, m), δ7.94 (1H, bq), δ9.88 (1H, s), δ10.98 (1H, s).

MS (APCI +ve): [M+H]⁺ at m/z 480 (C₂₅H₁₉F₂N₃O₃S requires [M+H]⁺ at 480).

Synthesis 3

3-[4-[3-(Aminocarbonylmethyl)phenylthio]phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example A3)

A solution of N-hydroxysuccinimide (1.0g, 8.70 mmol) in methanol (15mL) was treated with methanolic ammonia and the resulting ammonium salt was collected by filtration and dried in vacuo. A mixture of this ammonium salt (0.035 g, 0.27 mmol) and 3-[4-[3-(Carboxymethyl)phenylthio]phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Table A, Example A1; 0.100 g, 0.20 mmol) in dimethylformamide (5 mL) was cooled to 0°C and 1,3-dicyclohexylcarbodiimide (0.057 g, 0.27 mmol) was added. The mixture was allowed to warm to ambient temperature and stirred for 18 h. The dimethylformamide was removed in vacuo, the residue taken up in ethyl acetate (5 mL) and the insoluble material removed by filtration. The filtrate was concentrated and the residue chromatographed on silica gel using a gradient of dichloromethane-methanol as eluent to give a solid.

¹H NMR (DMSO-d₆): δ3.34 (2H, s), δ6.77 (3H, m), δ6.79 (1H, bs), δ7.09 (8H, m), δ7.42 (1H, bs), δ9.88 (1H, s), δ10.98 (1H, s).

MS (APCI +ve): [M+H]⁺ at m/z 466 (C₂₄H₁₇F₂N₃O₃S requires [M+H]⁺ at m/z 466).

30

Synthesis 4

3-[4-[3-(N-Hydroxyaminocarbonylmethyl)phenylthio]phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example A4)

O-(*tert*-Butyldimethylsilyl)hydroxylamine (0.029 g, 0.20 mmol) was added to a solution of 3-[4-[3-(Carboxymethyl)phenylthio]phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Table A, Example A1; 0.100 g, 0.20 mmol), 1-hydroxybenzotriazole (0.027 g, 0.20 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.041 g, 0.20 mmol in dichloromethane (5 mL). The mixture was stirred at ambient temperature for 18h. Water (5 mL) was added and the mixture extracted into ethyl acetate (3x10 mL). Concentration of the organic solutions gave a residue which was purified by chromatography on silica gel, eluting with a gradient of dichloromethane-methanol to give a solid.

¹H NMR (DMSO-d₆): δ3.30 (2H, s), δ6.78 (3H, m), δ7.10 (8H, m), δ8.85 (1H, s), δ9.88 (1H, s), δ10.63 (1H, s), δ10.98 (1H, bs).

MS (APCI +ve): [M+H]⁺ at m/z 482 (C₂₄H₁₇F₂N₃O₄S requires [M+H]⁺ at m/z 482).

Synthesis 5

5 3-[3-[(1,3-Thiazolidin-2,4-dion-5-yl)methyl]phenylamino]-4-(2,3,5-trifluorophenyl)-1H-pyrrole-2,5-dione (Example C1)

A solution of 5-[(3-aminophenyl)methyl]-1,3-thiazolidine-2,4-dione (277mg, 1.25 mmol) and 3-chloro-4-(2,3,5 trifluorophenyl)-1H-pyrrole-2,5-dione (131mg, 0.5mmol) in methanol (2 mL) was heated at 69°C for 5 days. EtOAc (6ml) was added and heating continued for a further 1hr. The mixture was acidified with aqueous hydrochloric acid (1M, 10mL) and extracted with ethyl acetate (10 mL). The organic solution was washed with water (3 x 10mL), brine, dried with magnesium sulphate, evaporated and the residue chromatographed on silica gel using dichloromethane-diethyl ether (gradient from 100:0 to 75:25 v/v) as eluent to afford the title compound, a solid.

¹H NMR (DMSO-d₆): δ2.75 (1H, dd), δ3.05 (1H, dd), δ4.67 (1H, dd), δ6.60-7.40 (6H, m), δ9.95 (1H, s), δ11.00 (1H, s) and δ12.05 (1H, br).

MS (APCI +ve): [M+H]⁺ at m/z 448 (C₂₀H₁₂F₃N₃O₄S requires [M+H]⁺ at m/z 448).

Synthesis 6

20 3-[[2-(2-Carboxyethyl)pyridin-5-yl]amino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example E1)

A mixture of 3-chloro-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (0.100 g, 0.41 mmol), 3-(5-aminopyridin-2-yl)propanoic acid (0.170 g, 1.02 mmol) and 1-methyl-2-pyrrolidinone (2.0 mL) was heated in a sealed tube in a hotblock set at 69°C for 14 days.

25 The mixture was diluted with water (100 mL) and extracted with ethyl acetate (2x60 mL). The combined organics were washed with water (80 mL), brine (80 mL), dried over anhydrous magnesium sulphate and evaporated to dryness. The residue was triturated with a mixture of dichloromethane-hexane (80:20 v/v) to afford the title compound, a solid.

30 ¹H NMR (DMSO-d₆): δ2.44-2.50 (2H, m), δ2.69-2.80 (2H, m), δ6.85-7.09 (4H, m), δ7.16-7.26 (1H, m), δ7.96 (1H, s), δ9.83 (1H, s), δ10.95 (1H,s) and δ12.05 (1H, br).

MS (APCI +ve): [M+H]⁺ at m/z 374 (C₁₈H₁₃F₂N₂O₄ requires [M+H]⁺ at m/z 374).

Synthesis 7

35 3-(3-Aminophenylamino)-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example C38)

3-(3-Nitrophenylamino)-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Table C, Example C36; 0.350 g, 1.01 mmol) and 10% Pd/C (50 mg) in ethanol (40 mL) was hydrogenated at atmospheric temperature and pressure for 2 hours. The reaction mixture was filtered through Kieselguhr and the filtrate concentrated in vacuo to give a solid which was triturated with a mixture of dichloromethane-hexane (20:80 v/v) to afford the title compound, a solid.

¹H NMR (DMSO-d₆): δ4.88 (2H, s), δ5.77 (1H, d), δ6.10-6.13 (2H, m), δ6.50 (1H, t), δ6.88-7.06 (2H, m), δ7.13-7.23 (1H, m), δ9.55 (1H, s), δ10.82 (1H, t). MS (APCI +ve): [M+H]⁺ at m/z 316 (C₁₆H₁₁F₂N₃O₂ requires [M+H]⁺ at m/z 316).

5 Synthesis 8

3-[4-(Benzoylamino)phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example A18)

- A mixture of 3-(4-aminophenylamino)-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Table C, Example C35; 0.100 g, 0.31 mmol), benzoic acid (0.042 g, 0.35 mmol), 10 1-hydroxybenzotriazole (0.047 g, 0.34 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.067 g, 0.34 mmol) in dimethylformamide (3 mL) was shaken on an orbital shaker for 72 hours. The mixture was diluted with aqueous hydrochloric acid (1M, 100 mL), and extracted with ethyl acetate (2x60 mL). The combined organic solutions were washed with saturated aqueous sodium bicarbonate (100 mL), brine (100 mL), dried over anhydrous magnesium sulphate and evaporated. Trituration of the residue with dichloromethane-hexane (20:80 v/v) gave the title product, a solid.
- 15 ¹H NMR (DMSO-d₆): δ6.77 (2H, d), δ6.96-7.17 (2H, m), δ7.17-7.27 (1H, d), δ7.40-7.60 (5H, m), δ7.88 (2H, d), δ9.75 (1H, s), δ10.00 (1H, s), δ10.85 (1H, br).
- 20 MS (APCI -ve): [M-H]⁻ at m/z 418 (C₂₃H₁₅F₂N₃O₃ requires [M-H]⁻ at m/z 418)

Synthesis 9

3-[4-(tert-Butoxycarbonylmethylcarbonylamino)phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example C49)

- 25 A mixture of 3-(4-aminophenylamino)-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Table C, Example C35; 0.100 g, 0.31 mmol), mono-tert-butyl malonate (0.056 g, 0.35 mmol), 1-hydroxybenzotriazole (0.047 g, 0.34 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.067 g, 0.34 mmol) in dimethylformamide (3 mL) was shaken on an orbital shaker for 72 hours. The mixture was diluted with dilute hydrochloric acid (100 mL), and extracted with ethyl acetate (2x60 mL). The combined organics were washed with saturated aqueous sodium bicarbonate (100 mL), brine (100 mL), dried over anhydrous magnesium sulphate and evaporated to dryness. The residue was chromatographed on silica gel using dichloromethane-diethyl ether (90:10 v/v) as eluent to afford the the title product, a solid.
- 30 ¹H NMR (DMSO-d₆): δ1.40 (9H, s), δ3.27 (2H, s), δ6.72 (2H, d), δ6.93-7.09 (2H, m), δ7.16-7.24 (3H, m), δ9.75 (1H, br), δ10.00 (1H, s), δ10.85 (1H, br).
- 35 MS (APCI -ve): [M-H]⁻ at m/z 456 (C₂₃H₂₁F₂N₃O₅ requires [M-H]⁻ at m/z 456).

Synthesis 10

40 3-[4-(Carboxymethylcarbonylamino)phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example C53)

- A mixture of 3-[4-(tert-butoxycarbonylmethylcarbonylamino)phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Table C, Example C49; 0.040 g, 0.087 mmol), trifluoroacetic acid (30 mL) and dichloromethane (50 mL) was stirred at

- room temperature for 40 minutes. The mixture was evaporated and the residue was diluted with water (80 mL), basified to ca. pH 3-4 with saturated aqueous sodium bicarbonate and extracted with ethyl acetate (2x70 mL). The combined organic solutions were quickly washed with saturated aqueous sodium bicarbonate (40 mL), brine (100 mL), dried over anhydrous magnesium sulphate and evaporated to dryness. The residue was triturated with a mixture of dichloromethane-hexane (20:80 v/v) to afford the title compound as a solid.
- 5 ^1H NMR (DMSO-d₆): δ 3.27 (2H, s), δ 6.72 (2H, d), δ 6.93-7.09 (2H, m), δ 7.17-7.26 (3H, m), δ 9.75 (1H, s), δ 10.03 (1H, s), δ 10.87 (1H, s), δ 12.60 (1H, br).
- 10 MS (APCI -ve): [M-H-CO₂]⁻ at m/z 356 (C₁₉H₁₃F₂N₃O₅ requires [M-H-CO₂]⁻ at m/z 356).

Synthesis 11

3-(2,3,4-Trifluorophenylamino)-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione

(Example C39)

A mixture of 2,3,4-trifluoroaniline (0.184 g, 1.25 mmol) and 3-chloro-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (0.122 g, 0.5 mmol) in 1-methyl-2-pyrrolidinone (2 mL) was heated in a sealed tube in a hotblock set at 69°C for 20 hours then at 90°C for a further 4 days. The mixture was diluted with aqueous hydrochloric acid (20 mL) and extracted with ethyl acetate (20 mL). The organics were washed with hydrochloric acid (20 mL), water (3x20 mL), and evaporated to dryness. The residue was chromatographed on silica gel using dichloromethane then dichloromethane-diethyl ether (50:1 v/v) as eluent to afford the title compound as a solid.

20 ^1H NMR (DMSO-d₆): δ 6.7 – 7.3 (6H, m), δ 9.8 (1H, br), δ 10.95 (1H, br).

25 MS (APCI +ve): [M+H]⁺ at m/z 355 (C₁₆H₇F₅N₂O₂ requires [M+H]⁺ at m/z 355).

Synthesis 12

3-[(2-Methylbenzoxazol-6-yl)amino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione

(Example B6) and

3-[(4-acetamido-3-hydroxyphenyl)amino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example C63)

A mixture of 6-amino-2-methylbenzoxazole (0.185 g, 1.25 mmol) and 3-chloro-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (0.122 g, 0.5 mmol) in methanol (3mL) was heated in a sealed tube in a hotblock set at 69°C for 20 hours. The mixture was diluted with aqueous hydrochloric acid (20 mL) and extracted with ethyl acetate (20 mL). The organics were washed with water (3x10 mL), and evaporated to dryness. The residue was triturated with diethyl ether to afford a solid which was dissolved in dichloromethane/methanol and chromatographed on silica gel using dichloromethane-diethyl ether (25:1 v/v) as eluent to afford 3-[(2-methylbenzoxazol-6-yl)amino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Table B, Example B6) as a solid.

35 ^1H NMR (DMSO-d₆): δ 2.50 (3H, s, obscured by DMSO solvent peak), δ 6.7 – 7.3 (6H, m), δ 10.0 (1H, br), δ 10.8 (1H, br).

40 MS (APCI +ve): [M+H]⁺ at m/z 356 (C₁₈H₁₁F₂N₃O₃ requires [M+H]⁺ at m/z 356).

Further elution of the chromatography column afforded 3-(3-hydroxy-4-acetamidophenylamino)-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Table C, Example C63) as a byproduct.

5 **Synthesis 13**

**3-(3-Trifluoromethyl-4-acetamidophenylamino)-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example C28) and
3-(3-trifluoromethyl-4-aminophenylamino)-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example C27)**

10 A solution of 3-trifluoromethyl-4-acetamidoaniline (273mg, 1.25 mmol) and 3-chloro-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (122mg, 0.5mmol) in methanol (2 mL) was heated at 69°C for 3 days. EtOAc (6ml) was added and heating continued for a further 1hr. The mixture was acidified with aqueous hydrochloric acid (1M, 10mL) and extracted with ethyl acetate (10 mL). The organic solution was washed with water (3 x 10mL), brine, dried with magnesium sulphate, evaporated and the residue chromatographed on silica gel using dichloromethane-diethyl ether (gradient from 100:0 to 75:25 v/v) as eluent to afford 3-(3-trifluoromethyl-4-acetamidophenylamino)-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Table C, Example C28) as a solid.
¹H NMR (DMSO-d₆): δ 1.97 (3H, s), δ 6.7-7.3 (6H, m), δ 9.37 (1H, s), δ 10.00 (1H, br), δ 10.92 (1H, br).

15 MS (APCI +ve): [M+H]⁺ at m/z 426 (C₁₉H₁₂F₅N₃O₃ requires [M+H]⁺ at m/z 426). Earlier fractions from the chromatography column yielded 3-(3-trifluoromethyl-4-aminophenylamino)-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Table C, Example C27) as a byproduct.

20

25 **Synthesis 14**

3-[2-(Methoxymethyl)indolin-1-yl]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example D6)

30 A solution of 3-chloro-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (195 mg, 0.80 mmol.), 2-(methoxymethyl)indoline (198 mg, 1.00 mmol.) and triethylamine (0.34 mL, 2.44 mmol.) in dry 1-methylpyrrolidin-2-one (3 mL) was heated under argon at 65 C for 3 days. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic solutions were washed with brine (2 x 20 mL), dried with magnesium sulphate, evaporated and the residue chromatographed on silica using a mixture of dichloromethane and diethyl ether as eluant to afford the title compound as a solid.

35 ¹H NMR (DMSO-d₆): δ 11.05 (1H, br), 7.36-7.13 (4H, m), 6.79 (1H, t), 6.61 (1H, t), 5.86 (1H, d), 5.26 (1H, m), 3.69 (1H, m), 3.35 (2H, m), 3.26 (3H, s), 3.00 (1H, dd).

40 MS (APCI+ve): [M+H]⁺ at m/z 371 (C₂₀H₁₆N₂O₃F₂ requires [M+H]⁺ at m/z 371).

Synthesis 15**3-[3-(4-Carboxyphenylaminocarbonylmethyl)phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example A50)**

A mixture of 4-(3-aminophenylacetylarnino)benzoic acid (0.277 g, 1.03 mmol), 3-chloro-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (0.100 g, 0.41 mmol) and 1-methyl-2-pyrrolidinone (2 mL) was heated at 110°C overnight before being diluted with dilute hydrochloric acid (2M, 150 mL) and extracted with ethyl acetate (3 x 80 mL). The combined ethyl acetate solutions were washed with brine, dried (MgSO_4) and evaporated. The residual solid was chromatographed on silica gel using dichloromethane-methanol (96:4 v/v) as eluent to afford the title compound, a solid.

$^1\text{H NMR}$ (DMSO-d₆): δ 3.30 (2H, s), δ 6.65-7.20 (7H, m), δ 7.66 (2H, d), δ 7.85 (2H, d), δ 9.75 (1H, s), δ 10.30 (1H, s), δ 10.85 (1H, s) and δ 12.62 (1H, s).

MS (AP-ve): [M]⁻ at m/z 477 ($\text{C}_{25}\text{H}_{17}\text{F}_2\text{N}_3\text{O}_5$ requires [M]⁻ at m/z 477).

Synthesis 16**3-[2-(Ethylamino)benzothiazol-6-ylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example B48)**

A solution of 2-ethylaminobenzothiazol-6-ylamine (316mg, 1.63mmol) and 3-chloro-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (158mg, 0.65mmol) in 1-methyl-2-pyrrolidinone (2mL) was allowed to stand at room temperature overnight. The mixture was diluted with aqueous hydrochloric acid (25mL) and extracted with ethyl acetate (35 mL). The organics were washed with water (3x25mL), and evaporated to dryness. The residue was triturated with dichloromethane to give a solid.

$^1\text{H NMR}$ (DMSO-d₆): δ 1.16 (3H,t), δ 3.31 (2H, m), δ 6.73 (1H, m), δ 6.95 (4H, m), δ 7.1 (1H, m), δ 7.86 (1H, t), δ 9.70(1H, bs), δ 10.80 (1H, bs).

MS (APCI +ve): [M+H]⁺ at m/z 401 ($\text{C}_{19}\text{H}_{14}\text{F}_2\text{N}_4\text{O}_2\text{S}$ requires [M+H]⁺ at m/z 401).

Synthesis 17**3-[3-(4-Pyrimidylaminocarbonylmethyl)phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example F17)**

A mixture of 4-aminopyrimidine (48mg, 0.5mmol), 3-[3-(carboxymethyl)-phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (prepared by analogy with Example Synthesis 1, 179mg, 0.5mmol), 1-hydroxybenzotriazole (68mg, 0.5mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (96mg, 0.5mmol) was dissolved in dimethylformamide (2mL). The solution was allowed to stand at room temperature for 5 days. Ethyl acetate (8mL), water (4mL) and saturated aqueous sodium bicarbonate (2 mL) were added, the layers separated and the organic layer washed with water then brine and evaporated to dryness. The residue was chromatographed on silica gel eluting with dichloromethane-methanol to give the product as a solid.

$^1\text{H NMR}$ (DMSO-d₆): δ 3.39 (2H, m), δ 6.6 – 7.2 (7H,m), δ 8.00 (1H, m), δ 8.6 (1H, m), δ 8.85 (1H, s), δ 9.76 (1H, s), δ 10.9 (1H, s) and δ 11.0 (1H, s).

MS (APCI +ve): [M+H]⁺ at m/z 436 ($\text{C}_{22}\text{H}_{15}\text{F}_2\text{N}_5\text{O}_3$ requires [M+H]⁺ at 436).

Synthesis 18

3-[3-(3-Carboxyphenylaminocarbonylmethyl)phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example A91)

A mixture of 3-[3-(carboxymethyl)phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (prepared by analogy with Example Synthesis 1, 179mg, 0.5mmol), 1-

- 5 hydroxybenzotriazole (68mg, 0.5mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (96mg, 0.5mmol) was dissolved in dimethylformamide (2mL). After standing at room temperature for 1 hour, 3-aminobenzoic acid (69mg, 0.5mmol) was added and the resulting solution was allowed to stand at room temperature for 2 days. Ethyl acetate (8mL) and water (6mL) were added, the layers separated and the 10 organic layer washed with water (3x6mL) and evaporated to a gum which was triturated with dichloromethane/methanol to give the product as a solid.

¹H NMR (DMSO-d₆): δ3.28 (2H, s), δ6.73 (2H, m), δ6.95 (4H, m), δ7.15 (1H, m), δ7.41 (1H, m), δ7.60 (1H, m), δ7.80 (1H, m), δ8.19 (1H, s), δ9.77 (1H, s), δ10.2 (1H, s), δ10.9 (1H, s), δ12.9 (1H, bs).

- 15 MS (APCI -ve): [M]⁻ at m/z 477 (C₂₅H₁₇F₂N₃O₅ requires [M]⁻ at 477).

Synthesis 19

3-(3,5-Difluorophenylamino)-4-(4-acetylaminophenyl)-1H-pyrrole-2,5-dione (Example C97)

- 20 A mixture of 3-(3,5-difluorophenylamino)-4-(4-nitrophenyl)-1H-pyrrole-2,5-dione (Table C, Example C91, 0.012 g, 0.035 mmol), stannous chloride dihydrate (0.023 g, 0.105 mmol) and ethanol (5 mL) was stirred at 70°C overnight before being evaporated and suspended in dichloromethane. The resulting precipitate was collected and suspended in dichloromethane (5 mL) and treated with acetic anhydride (10 uL, 0.1 mmol). The mixture was stirred for 70 hours then chromatographed on silica gel using dichloromethane-methanol (90:10 v/v) as eluent to afford the title compound, a solid.

¹H NMR (DMSO-d₆): δ2.02 (3H, s), δ6.33 (2H, m), δ6.65 (1H, m), δ6.98 (2H, d), δ7.41 (2H, s), δ9.60 (1H, bs), δ9.90 (1H, s) and δ10.90 (1H, s).

MS (AP-ve): [M]⁻ at m/z 357 (C₁₈H₁₃F₂N₂O₃ requires [M]⁻ at m/z 357).

30

Synthesis 20

3-(Indolin-5-ylamino)-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example B46)

- A mixture of 3-(N-t-butoxycarbonylindolin-5-ylamino)-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Table B, Example B45, 0.100 g, 0.22 mmol), trifluoroacetic acid (0.5 mL) and dichloromethane (9.5 mL) was stirred at room temperature for 2 hours, then 35 evaporated. The residue was azeotroped from dichloromethane (x3) to afford the product, a solid.

¹H NMR (DMSO-d₆): δ2.73 (2H, t), δ3.55 (2H, t), δ3.98 (1H, br), δ6.60-7.30 (6H, m), δ9.77 (1H, s), and δ10.90 (1H, s).

- 40 MS (AP+ve): [M+H]⁺ at m/z 342 (C₁₈H₁₃F₂N₃O₂ requires [M+H]⁺ at m/z 342).

Synthesis 21

3-[3-(N-Hydroxylaminocarbonylmethyl)phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example C106)

A mixture of O-(tert-butyldimethylsilyl)hydroxylamine (221mg, 1.5mmol), 3-[3-(carboxymethyl)phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (prepared by analogy with Example Synthesis 1, 179mg, 0.5mmol), 1-hydroxy-7-azabenzotriazole (136mg, 1mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (144mg, 0.75mmol) was dissolved in dimethylformamide (2mL). The solution was allowed to stand at room temperature for 4 days. Ethyl acetate (8mL) and water (8mL) were added and the mixture acidified to pH3 with dilute hydrochloric acid. The layers were separated and the organic layer washed with water (2x8mL), saturated aqueous sodium bicarbonate (8mL) then water (2x8mL) and evaporated to dryness. The residue was chromatographed on silica gel eluting with dichloromethane-methanol to give a solid (38mg). This was dissolved in tetrahydrofuran (3mL), tetrabutylammonium fluoride trihydrate (49mg, 0.156mmol) added and the solution stirred at room temperature for 30 mins. The resulting suspension was evaporated to dryness, the residue dissolved in ethyl acetate (10mL) and water (10mL) and acidified to pH3 with dilute hydrochloric acid. The layers were separated and the organic layer washed with water (2x10mL) and evaporated to give the product as a solid.

¹H NMR (DMSO-d₆): δ2.87 (2H, s), δ6.61 (1H, s), δ6.71 (1H, m), δ6.81 (1H, m), δ7.0 (3H, m), δ7.15 (1H, m), δ8.74 (1H, bs) and δ9-11 (3H, broad).

MS (APCI -ve): [M-H]⁻ at m/z 372 (C₁₈H₁₃F₂N₃O₄ requires [M-H]⁻ at 372).

20

Synthesis 22

3-[3-(2-(4-Aminophenylsulphonyl)ethoxycarbonylmethyl)phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example A70)

A mixture of 2-(4-aminophenylsulphonyl)ethanol hydrochloride (119mg, 0.5mmol), 3-[3-(carboxymethyl)phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (179mg, 0.5mmol), 1-hydroxybenzotriazole (68mg, 0.5mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (96mg, 0.5mmol) and triethylamine (101mg, 1mmol) in dimethylformamide (2mL) was well shaken then allowed to stand at room temperature for 3days. Ethyl acetate (8mL), water (4mL) and saturated aqueous sodium bicarbonate (2 mL) were added, the layers separated and the organic layer washed with water then brine and evaporated to dryness. The residue was chromatographed on silica gel eluting with dichloromethane-methanol to give the product as a solid.

¹H NMR (DMSO-d₆): δ2.99 (2H, s), δ3.57 (2H, t), δ4.23 (2H, t), δ5.69 (2H, s), δ6.49 (1H, s), δ6.75 (2H, m), δ6.8-7.1 (6H, m), δ7.1-7.3 (2H, m) δ9.73 (1H, s), δ10.9 (1H, s).

MS (APCI +ve): [M+H]⁺ at m/z 542 (C₂₆H₂₁F₂N₃O₆ S requires [M+H]⁺ at 542).

The following additional methods (Methods 1 and 2) serve to illustrate a typical preparation of a non-commercial aniline by a method analogous to that described in *Synthesis* 1994, 1413.

5

Method 1**3-[(4-Nitrophenyl)thio]benzoic acid**

- A suspension of potassium carbonate (18g) in acetone (140 mL) at ambient temperature was treated with 3-mercaptopbenzoic acid (10g, 64.4 mmol, 1 eq) followed by 4-nitrofluorobenzene (18g, 127.7 mmol, 2 eq). The resultant mixture was stirred for 18h and then poured onto saturated sodium bicarbonate and washed with ethyl acetate. The basic aqueous layer was acidified with 5N HCl and extracted into ethyl acetate (3x100 mL). The combined organics were dried with anhydrous sodium sulphate and concentrated *in vacuo* to give the product as a solid.
- 15 ^1H NMR (DMSO): δ 7.35 (2H, d), 7.66 (1H, t), 7.81 (1H, m), 8.06 (2H, m), 8.16 (2H, d), and 13.31 (1H, bs).
- MS (APCI-ve): [M-H]⁻ at m/z 274 ($\text{C}_{13}\text{H}_9\text{NO}_4\text{S}$ requires [M-H]⁻ at m/z 274)

10

Method 2

20

3-[(4-Aminophenyl)thio]benzoic acid

- A mixture of 3-[(4-nitrophenyl)thio]benzoic acid (11.2g, 40.7 mmol) and 10% Pd/C (0.5g) in ethanol (250 mL) was hydrogenated at atmospheric temperature and pressure for 24h. The mixture was filtered through Celite and concentrated *in vacuo* to give the required aniline as a solid. ^1H NMR (DMSO): δ 5.59 (2H, bs), 6.64 (2H, d), 7.28 (3H, m), 7.37 (1H, t), 7.52 (1H, s), 7.65 (1H, d), and 12.32 (1H, bs). MS (APCI+ve): [M+H]⁺ at m/z 246 ($\text{C}_{13}\text{H}_{11}\text{NO}_2\text{S}$ requires [M+H]⁺ at m/z 246).

25

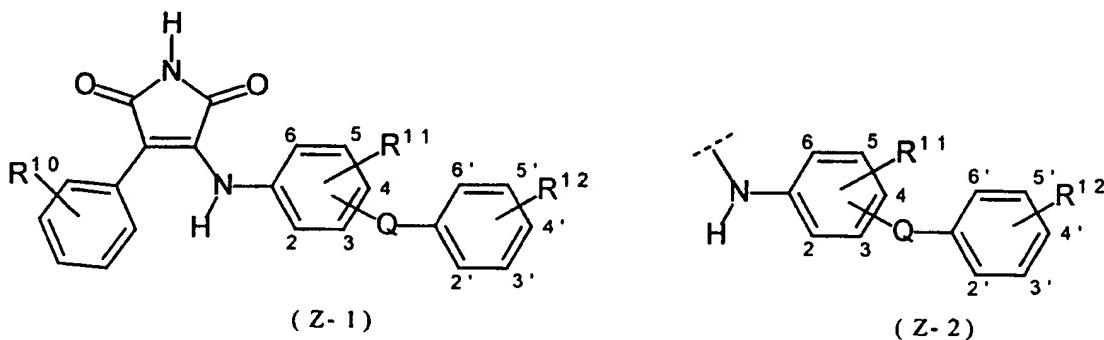
The further examples described herein were prepared according to the methods disclosed herein, with particular reference to Example Syntheses 1 to 22 above. Example Syntheses 1 to 22 themselves are shown as Example Compounds in the following Tables according to the list below:

5

| Synthesis No. | Table | Example No. |
|----------------|-------|-------------|
| 1 | A | A1 |
| 2 | A | A2 |
| 3 | A | A3 |
| 4 | A | A4 |
| 5 | C | C1 |
| 6 | E | E1 |
| 7 | C | C38 |
| 8 | A | A18 |
| 9 | C | C49 |
| 10 | C | C53 |
| 11 | C | C39 |
| 12 | B | B6 |
| 12 (Byproduct) | C | C63 |
| 13 | C | C28 |
| 13 (Byproduct) | C | C27 |
| 14 | D | D6 |
| 15 | A | A50 |
| 16 | B | B48 |
| 17 | F | F17 |
| 18 | A | A91 |
| 19 | C | C97 |
| 20 | B | B46 |
| 21 | C | C106 |
| 22 | A | A70 |

Table A

5 Encompassing compounds of general formula (Z-1), wherein group R² of formula (I) is a phenyl ring, optionally substituted by one or more substituents R¹⁰ and the moiety NR¹R³ of formula (I) is represented by a moiety of general formula (Z-2), optionally substituted by one or more substituents R¹¹ and one or more substituents R¹², and Q represents a linking moiety as hereinbefore defined. The positions of substitution of R¹¹, R¹² and Q are defined with reference to formula (Z-2) and the values of R¹⁰, R¹¹, R¹² and Q are
10 listed in Table A.



| Exa mple No. | R ^I | R ^{II} | Q | R ^{IV} | [M+H] ⁺ Observed; (Unless [M] ⁻ or [M-H] ⁻ are Indicated) | For Procedure See Example No. |
|--------------------|----------------|-----------------|-------|--|--|---|
| A1 | 2,3-di-F | H | 4-[S] | 3'- CH ₂ CO ₂ H | 467 | 1 |
| A2 | 2,3-di-F | H | 4-[S] | 3'- CH ₂ CONH Me | 480 | 2 |
| A3 | 2,3-di-F | H | 4-[S] | 3'- CH ₂ CONH ₂ | 466 | 3 |
| A4 | 2,3-di-F | H | 4-[S] | 3'- CH ₂ CONHO H | 482 | 4 |

| | | | | | | |
|-----|----------|----------------------|--------------------------|-----------------------------------|------------|---|
| A5 | 2,3-di-F | H | 4-[S] | 3'-CONHMe | 466 | 2 |
| A6 | 2,3-di-F | 3-CO ₂ H | 4-[S] | 3'-CONHMe | 510 | 2 |
| A7 | 2,3-di-F | H | 4-[O] | 3'-CO ₂ H | 437 | 1 |
| A8 | 2,3-di-F | H | 3-[CH ₂ CONH] | H | 432 [M-H]- | 5 |
| A9 | 2,3-di-F | H | 4-[CH ₂ CONH] | H | 434 | 5 |
| A10 | 2,3-di-F | H | 3-[CO] | H | 405 | 5 |
| A11 | 2,3-di-F | H | 3-[OCH ₂] | H | 407 | 5 |
| A12 | 2,3-di-F | H | 4-[NHCO] | 2'-OH | 436 | 5 |
| A13 | 2,3-di-F | 3-CO ₂ Et | 4-[S] | 2'-CO ₂ H | 525 | 5 |
| A14 | 2,3-di-F | H | 4-[O] | 3'-CONHMe | 450 | 2 |
| A15 | 2,3-di-F | H | 4-[O] | 3'-CONH ₂ | 434[M-H]- | 3 |
| A16 | 2,3-di-F | H | 4-[S] | 3'-CONH ₂ | 452 | 3 |
| A17 | 2,3-di-F | H | 4-[O] | 4'-CONHMe | 450 | 5 |
| A18 | 2,3-di-F | H | 4-[NHCO] | H | 418 [M-H]- | 8 |
| A19 | 2,3-di-F | H | 4-[S] | 3'-CONH(CH ₂) 2OMe | 510 | 2 |
| A20 | 2,3-di-F | 3-CO ₂ H | 4-[S] | 2'-CO ₂ H | 495 [M-H]- | 1 |
| A21 | 2,3-di-F | H | 4-[NHCOC ₂ H] | H | 434 | 8 |
| A22 | 2,3-di-F | H | 3-[NHCOC ₂ H] | H | 432 [M-H]- | 8 |
| A23 | 2,3-di-F | H | 3-[NHCO] | H | 418 [M-H]- | 8 |
| A24 | 2,3-di-F | H | 4-[O] | 4'-CO ₂ H | 437 | 5 |
| A25 | 2,3-di-F | 3-CO ₂ H | 4-[S] | H | 453 | 1 |

| | | | | | | |
|-----|----------|-------------------------|---|--|------------|---|
| A26 | 2,3-di-F | H | 4-[CH ₂ NHCOC H ₂] | H | 446 [M-H]- | 8 |
| A27 | 2,3-di-F | 3- CONH Me | 4-[S] | H | 466 | 2 |
| A28 | 2,3-di-F | H | 4-[O] | 4'-CONH ₂ | 436 | 3 |
| A29 | 2,3-di-F | H | 4-[S] | 3'- [CH ₂ CONH(CH ₂) ₂ - Morpholin-4- yl] | 579 | 1 |
| A30 | 2,3-di-F | H | 3-[SO ₂ NH] | H | 456 | 5 |
| A31 | 2,3-di-F | H | 3- [CH ₂ NHCO] | H | 432 [M-H]- | 8 |
| A32 | 2,3-di-F | H | 4-[NHSO ₂] | 4'-Me | 468 [M-H]- | 1 |
| A33 | 2,3-di-F | H | 3- [CH ₂ NHCOC H ₂] | H | 446 [M-H]- | 8 |
| A34 | 2,3-di-F | H | 4- [NHCOC ₂ CH ₂ C H ₂] | H | 446 [M-H]- | 8 |
| A35 | 3-CN | H | 4-[S] | 3'-CO ₂ H | 440 [M-H]- | 1 |
| A36 | 2,3-di-F | H | 4-[O] | 2'-CO ₂ H | 437 | 1 |
| A37 | 2,3-di-F | 3- CO ₂ H | 4-[bond] | H | 419 [M-H]- | 1 |
| A38 | 2,3-di-F | H | 4-[S] | 2'- CH ₂ CO ₂ Me | 481 | 1 |
| A39 | 2,3-di-F | H | 4-[S] | 4'-CONH ₂ | 452 | 3 |
| A40 | 2,3-di-F | 3- CO ₂ H | 4-[S] | 4'-CO ₂ H | 495 [M-H]- | 1 |

| | | | | | | |
|-----|-------------|---------------------|--|--------------------------------------|----------------|----|
| A41 | 2,3-di-F | H | 4-[O] | 2'-CONHMe | 448 [M-H]- | 2 |
| A42 | 2,3-di-F | H | 4-[CH ₂ CONH] | 3'-CO ₂ H | 476 [M-H]- | 1 |
| A43 | 2,3-di-F | H | 4-[O] | 3'-CH ₂ CO ₂ H | 451 | 1 |
| A44 | 2,3-di-F | H | 4-[S] | 2'-CO ₂ H | 451 [M-H]- | 1 |
| A45 | 2,3-di-F | H | 4-[O] | 2'-CONH ₂ | 435 [M]- | 2 |
| A46 | 2,3-di-F | H | 4-[S] | 4'-CONHMe | 466 | 2 |
| A47 | 2,3-di-F | H | 4-[S] | 2'-CONH ₂ | 451 [M]- | 3 |
| A48 | 2,3-di-F | H | 4-[S] | 2'-CONHMe | 464 [M-H]- | 2 |
| A49 | 2,3-di-F | H | 4-[CH ₂ CONH] | 4'-CO ₂ H | 477 [M]- | 15 |
| A50 | 2,3-di-F | H | 3-[CH ₂ CONH] | 4'-CO ₂ H | 477 [M]- | 15 |
| A51 | 2,3-di-F | 3-CO ₂ H | 4-[O] | H | 436 [M]- | 15 |
| A52 | 2,3-di-F | 3-CO ₂ H | 4-[O] | 4'-Ph | 512 [M]- | 15 |
| A53 | 2,3-di-F | H | 3-[CONH] | 4'-CO ₂ H | 462 [M-H]- | 15 |
| A54 | 2,3-di-F | H | 3-[CH ₂ O] | 4'-CO ₂ H | 449 [M-H]- | 1 |
| A55 | 2,3-di-F | H | 4-[CH ₂ SO ₂ NH] | H | 468 [M-H]- | 5 |
| A56 | 2-F-3-Cl | H | 4-[O] | 4'-CO ₂ H | 451/453 [M-H]- | 1 |
| A57 | 2,3-di-F | H | 3-[O] | 4'-CO ₂ H | 435 [M-H]- | 1 |
| A58 | 2,3-di-F | H | 3-[O] | 4'-CH ₂ CO ₂ H | 451 | 15 |
| A59 | 2,3-di-F | H | 4-[O] | 4'-CH ₂ CO ₂ H | 449 [M-H]- | 15 |
| A60 | 2,3,6-tri-F | H | 4-[O] | 4'-CO ₂ H | 453 [M-H]- | 1 |

| | | | | | | |
|-----|----------|---|---|--|-----------------|----|
| A61 | 2,3-di-F | H | 3-[CH ₂ CONH] | 4'-CH ₂ CH ₂ OH | 478 | 17 |
| A62 | 2-Cl-3-F | H | 4-[O] | 4'-CO ₂ H | 451, 453 [M-H]- | 1 |
| A63 | 2,3-di-F | H | 3-[O] | 3'-CO ₂ H | 437 | 15 |
| A64 | 2,3-di-F | H | 3-[O] | 4'-CH ₂ CH ₂ CO ₂ H | 465 | 15 |
| A65 | 2,3-di-F | H | 3-[CH ₂ CONH] | 4'-Morpholin-4-yl | 519 | 17 |
| A66 | 2,3-di-F | H | 3-[CH ₂ CONH] | 4'-Piperidin-1-yl | 517 | 17 |
| A67 | 2,3-di-F | H | 3-[CH ₂ CONH] | 4'-CH ₂ OH | 463 [M-H]- | 17 |
| A68 | 2,3-di-F | H | 4-[O] | 3'-NMe ₂ | 436 | 1 |
| A69 | 2,3-di-F | H | 3-[OCH ₂] | 4'-CO ₂ H | 449 [M-H]- | 1 |
| A70 | 2,3-di-F | H | 3-[CH ₂ CO ₂ -CH ₂ CH ₂ SO ₂] | 4'-NH ₂ | 542 | 22 |
| A71 | 2,3-di-F | H | 3-[CH ₂ CONH] | 4'-NMe ₂ | 477 | 17 |
| A72 | 2,3-di-F | H | 3-[CH ₂ CONH] | 3'-Cl-4'-Morpholin-4-yl | 552/554 [M-H]- | 17 |
| A73 | 2,3-di-F | H | 3-[CH ₂ CONH] | 4'-CH ₂ CN | 473 | 17 |
| A74 | 2,3-di-F | H | 3-[CH ₂ CONH] | 4'-OCH ₂ -(1-Me-Piperidin-4-yl) | 561 | 17 |

| | | | | | | |
|-----|----------|------|------------------|------------------|--------------------|----|
| A75 | 2,3-di-F | H | 3-[O] | 3'-NH2 | 408 | 1 |
| A76 | 2,3-di-F | H | 4-[O] | 4-NHCOMe | 450 | 1 |
| A77 | 2,3-di-F | 3-Me | 4-[O] | 4'- CH2CO2H | 464 [M]- | 1 |
| A78 | 2,3-di-F | H | 4- [CH2SO2NH] | 4'-CO2H | 512 [M-H]- | 1 |
| A79 | 2,3-di-F | H | 4-[O] | 3'-NHCOMe | 450 | 1 |
| A80 | 2,3-di-F | H | 3- [CH2CONH] | 3'-NHCOMe | 491 | 17 |
| A81 | 2,3-di-F | H | 3- [CH2CONH] | 4'-NHCOMe | 491 | 17 |
| A82 | 2,3-di-F | H | 3- [CH2CONH] | 4'- N(Me)COMe | 504 [M-] | 17 |
| A83 | 2,3-di-F | H | 3- [CH2CONH] | 3'-CONH2 | 477 | 17 |
| A84 | 2,3-di-F | H | 3- [CH2CONH] | 2'-CONH2 | 476 [M-] | 17 |
| A85 | 2,3-di-F | H | 3- [CH2CONH] | 3'-NMe2 | 477 | 17 |
| A86 | 2,3-di-F | H | 4- [CH2SO2NH] | 4'- CH2CO2H | 526 [M-H]- | 1 |
| A87 | 2,3-di-F | H | 4- [CH2SO2NH] | 3'- CH2CO2H | 526 [M-H]- | 1 |
| A88 | 2,3-di-F | H | 4- [CH2SO2NH] | 3'-CO2H | 512 [M-H]- | 1 |
| A89 | 2,3-di-F | 3-Cl | 4-[O] | 4'- CH2CO2H | 483/485 [M- H]- | 1 |
| A90 | 2,3-di-F | 3-Cl | 4-[O] | 4'-CO2H | 469/471 [M- H]- | 1 |
| A91 | 2,3-di-F | H | 3- [CH2CONH] | 3'-CO2H | 477 [M-] | 18 |

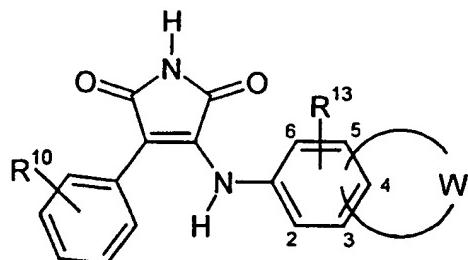
| | | | | | | |
|------|----------|---------------------|--|---|-------------|----|
| A92 | 2,3-di-F | H | 3-[CH ₂ CONHC ₂ H ₅] | 4'-NMe ₂ | 491 | 17 |
| A93 | 2,3-di-F | H | 3-[CH ₂ CONHNHCO] | 4'-NH ₂ | 491 [M-] | 17 |
| A94 | 2,3-di-F | H | 4-[O] | 4'-CH ₂ NHCO ₂ Me | 464 | 1 |
| A95 | 4-Cl | 3-CO ₂ H | 4-[O] | 4'-Cl | 469/471/473 | 5 |
| A96 | 2,3-di-F | H | 3-[O] | 4'-NHCOMe | 450 | 1 |
| A97 | 2,3-di-F | H | 3-[CH ₂ CONH] | 4'-CONH ₂ | 475 [M-H]- | 17 |
| A98 | 2,3-di-F | H | 4-[O] | 3'-NHCONH ₂ | 449 [M-H]- | 1 |
| A99 | 2,3-di-F | H | 4-[O] | 4'-CH ₂ CH ₂ NMe ₂ | 464 | 1 |
| A100 | 2,3-di-F | H | 3-[CH ₂ CONH] | 3'-NH ₂ | 449 | 17 |
| A101 | 2,3-di-F | H | 3-[CH ₂ CONH] | 4'-NH ₂ | 449 | 17 |
| A102 | 2,3-di-F | H | 3-[CH ₂ CONHNHCO] | H | 477 | 17 |
| A103 | 2,3-di-F | H | 3-[CH ₂ CONH] | 4'-SO ₂ NH ₂ | 513 | 17 |
| A104 | 2,3-di-F | H | 3-[CH ₂ CONH] | 3'-CH ₂ OH | 462 [M-H]- | 17 |

| | | | | | | |
|------|----------|---|--|------------------------------------|------------------------|----|
| A105 | 2,3-di-F | H | 3-[CH ₂ CONH(CH ₂) ₂] | 4'-NH ₂ | 477 | 17 |
| A106 | 2,3-di-F | H | 3-[CH ₂ CONHNHCO] | 3'-NH ₂ | 492 | 17 |
| A107 | 2,3-di-F | H | 3-[CH ₂ SO ₂ NH] | H | 468 [M-H] ⁻ | 1 |
| A108 | 2,3-di-F | H | 3-[CH ₂ SO ₂ NH] | 3'-CO ₂ H | 512 [M-H] ⁻ | 1 |
| A109 | 2,3-di-F | H | 3-[CH ₂ CONH] | 4'-NHSO ₂ Me | 527 | 17 |
| A110 | 2,3-di-F | H | 3'-[CH ₂ SO ₂ NH] | 4'-CO ₂ H | 512 [M-H] ⁻ | 1 |
| A111 | 2,3-di-F | H | 3-[SO ₂] | 3'-NH ₂ | 456 | 1 |
| A112 | 2,3-di-F | H | 4-[O] | 4'-SO ₂ NH ₂ | 470 [M-H] ⁻ | 1 |
| A113 | 2,3-di-F | H | 4-[O] | 4'-NH ₂ | 406 [M-H] ⁻ | 1 |
| A114 | 2,3-di-F | H | 4-[CH ₂ SO ₂ NH] | 4'-NHSO ₂ Me | 563 | 1 |
| A115 | 2,3-di-F | H | 4-[CH ₂ SO ₂ NH] | 4'-NHCOMe | 525 [M-H] ⁻ | 1 |

Table B

Encompassing compounds of general formula (Z-3), wherein group R² of formula (I) is a phenyl ring, optionally substituted by one or more substituents R¹⁰ and the group R¹ is represented by a benzene ring fused to an additional ring wherein the moiety W represents the atoms which, when taken together with the atoms of the benzene ring to which they are attached, form the fused ring. The position of the fusion of the two rings is defined with reference to the atom numbering depicted in formula (Z-3), for example in the case of compound B1, the moiety W has the value 3,4-[S-CH=N] and is defined as having the sulphur atom of the moiety attached at position 3 and the nitrogen atom attached at position 4 to form a 5-membered thiazole ring. Additionally, the benzene ring may be optionally substituted by one or more additional substituents R¹³. The group R³ of formula (I) is hydrogen. The values of R¹⁰, R¹³ and W are listed in Table B.

15



(Z-3)

| Example No. | R ¹⁰ | R ¹³ | W | [M+H] ⁺ Observed; (Unless [M] ⁻ or [M-H] ⁻ are Indicated) | For Procedure See Example No. |
|-------------|-----------------|-----------------|---|--|----------------------------------|
| B1 | 3-CN | H | 3,4-[S-CH=N] | 347 | 5 |
| B2 | 2,3-di-F | H | 3,4-[CH ₂ CH ₂ N(SO ₂ Me)] | 420 | 5 |
| B3 | 2,3,6-tri-F | H | 3,4-[CH ₂ CH ₂ CH ₂] | 359 | 5 |
| B4 | 2,3-di-F | H | 3,4-[N=C(Me)-S] | 372 | 5 |
| B5 | 2,3-di-F | H | 3,4-[S-C(Me)=N] | 372 | 5 |

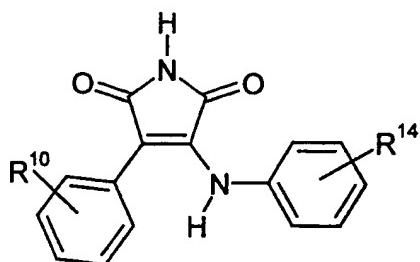
| | | | | | |
|-----|----------|---|--------------------------|----------------|----|
| B6 | 2,3-di-F | H | 3,4-[O-C(Me)=N] | 356 | 12 |
| B7 | 2,3-di-F | H | 3,4-[N=C(Me)-O] | 356 | 1 |
| B8 | 2,3-di-F | H | 3,4-[O-CH=N] | 342 | 1 |
| B9 | 2,3-di-F | H | 3,4-[CH=CH-N(Me)] | 354 | 1 |
| B10 | 2,3-di-F | H | 3,4-[O-C(=O)-NH] | 358 | 1 |
| B11 | 3-CO2H | H | 3,4-[S-CH=N] | 364 [M-H]- | 1 |
| B12 | 2,3-di-F | H | 3,4-[S-C(SCH2CO2Me)=N] | 462 | 5 |
| B13 | 2,3-di-F | H | 3,4-[S-C(SCH2CO2H)=N] | 448 | 1 |
| B14 | 3-CH2OH | H | 3,4-[S-CH=N] | 350 [M-H]- | 5 |
| B15 | 2,3-di-F | H | 3,4-[CH=CH-CH=N] | 352 | 1 |
| B16 | 2,3-di-F | H | 3,4-[S-C(=O)-NH] | 372 [M-H]- | 1 |
| B17 | 2,3-di-F | H | 3,4-[N(Me)-CH=N] | 355 | 1 |
| B18 | 2,3-di-F | H | 3,4-[S-C(Cl)=N] | 392/394 | 1 |
| B19 | 2,3-di-F | H | 3,4-[S-C(SMe)=N] | 404 | 14 |
| B20 | 2-F-3-Cl | H | 3,4-[S-CH=N] | 372/374 [M-H]- | 5 |
| B21 | 2,3-di-F | H | 3,4-[NHCONH] | 357 | 14 |
| B22 | 2,3-di-F | H | 3,4-[S-C(Ph)=N] | 434 | 1 |
| B23 | 2,3-di-F | H | 3,4-[S-C(NHMe)=N] | 387 | 14 |
| B24 | 2,3-di-F | H | 3,4-[S-C(NMe2)=N] | 401 | 1 |
| B25 | 2,3-di-F | H | 3,4-[S-C(=O)N(CH2CO2Me)] | 446 | 1 |
| B26 | 2,3-di-F | H | 3,4-[S-C(=O)N(CH2CO2H)] | 432 | 1 |
| B27 | 2,3-di-F | H | 3,4-[CH=CH-S] | 357 | 1 |
| B28 | 2,3-di-F | H | 3,4-[S-C[S(CH2)3CO2H]=N] | 476 | 1 |

| | | | | | |
|-----|-------------|---|--|------------|----|
| B29 | 2,3-di-F | H | 3,4-[S-C(NHPh)=N] | 449 | 1 |
| B30 | 2,3-di-F | H | 3,4-[N(Me)CON(Me)] | 385 | 1 |
| B31 | 2,3-di-F | H | 3,4-[S-CO-N(Me)] | 388 | 1 |
| B32 | 2,3-di-F | H | 3,4-[S-C[(CH ₂) ₄ CO ₂ Me]=N] | 472 | 1 |
| B33 | 2,3-di-F | H | 3,4-[S-C[(CH ₂) ₄ CO ₂ H]=N] | 458 | 1 |
| B34 | 2-Cl-3-F | H | 3,4-[S-CH=N] [M-H]- | 372/374 | 5 |
| B35 | 2,3,6-tri-F | H | 3,4-[S-CH=N] [M-H]- | 374 [M-H]- | 5 |
| B36 | 2,3-di-F | H | 3,4-[CH=C(CO ₂ H)-O] | 384 [M]- | 1 |
| B37 | 2,3-di-F | H | 3,4-[S-C[NH(CH ₂) ₃ NMe ₂]=N] | 458 | 16 |
| B38 | 2,3-di-F | H | 3,4-[S-CO-N[(CH ₂) ₃ NMe ₂]] | 459 | 1 |
| B39 | 2,3-di-F | H | 3,4-[S-C(Morpholin-4-yl)=N] | 443 | 1 |
| B40 | 2,3-di-F | H | 3,4-[S-CO-N(3-F-Ph)] | 468 | 15 |
| B41 | 2,3-di-F | H | 3,4-[S-CO-N(4-OMe-Ph)] | 480 | 15 |
| B42 | 2,3-di-F | H | 3,4-[S-CO-N(CH ₂ Ph)] | 464 | 5 |
| B43 | 2,3-di-F | H | 3,4-[S-CO-N(3-NHCOMe-Ph)] | 507 | 1 |
| B44 | 2,3-di-F | H | 3,4-[CH=C(CO ₂ H)-N(Me)] | 396 [M-H]- | 1 |
| B45 | 2,3-di-F | H | 3,4-[CH ₂ CH ₂ N(CO ₂ t-Bu)] | 440 [M-H]- | 5 |
| B46 | 2,3-di-F | H | 3,4-[CH ₂ CH ₂ NH] | 342 | 20 |
| B47 | 2,3-di-F | H | 3,4-[CH ₂ CONH] | 356 | 1 |
| B48 | 2,3-di-F | H | 3,4-[S-C(NHEt)=N] | 401 | 16 |

| | | | | | |
|-----|----------|---|-----------------------------|----------------|----|
| B49 | 2,3-di-F | H | 3,4-[S-C(NH2)=N] | 373 | 1 |
| B50 | 2,3-di-F | H | 3,4-[S-C(NH-i-Pr)=N] | 415 | 1 |
| B51 | 2,3-di-F | H | 3,4-[NH-CO-O] | 358 | 1 |
| B52 | 2,3-di-F | H | 3,4-[CH=C(CONH2)- N(Me)] | 395 [M- H]- | 1 |
| B53 | 2,3-di-F | H | 3,4-[OCH2CONH] | 370 [M- H]- | 14 |
| B54 | 2,3-di-F | H | 3,4-[S- C(NHCOMe)=N] | 415 | 1 |

Table C

5 Encompassing compounds of general formula (Z-4), wherein group R² of formula (I) is a phenyl ring, optionally substituted by one or more substituents R¹⁰, group R¹ of formula (I) is a phenyl ring, optionally substituted by one or more substituents R¹⁴ and group R³ of formula (I) is hydrogen, and substituents R¹⁰ and R¹⁴ are listed in Table C.



10

(Z-4)

| Example No. | R ¹⁰ | R ¹⁴ | [M+H] ⁺ Observed; (Unless [M] ⁻ or [M-H] ⁻ are Indicated) | For Procedure See Example No. |
|-------------|-----------------|---|---|-------------------------------------|
| C1 | 2,3,5-tri-F | 3-[CH ₂ -(1,3-thiazolidine-2,4-dion-5-yl)] | 448 | 5 |
| C2 | 3,5-di-Me | 3,5-di-F | 327 [M-H] ⁻ | 5 |
| C3 | 2,3,6-tri-F | 3-Cl | 353/355 | 5 |
| C4 | 2,3-di-F | 3-OCH ₂ CO ₂ H | 375 | 1 |
| C5 | 3-CN | H | 290 | 5 |
| C6 | 3-CN | 3,5-di-F | 324 [M-H] ⁻ | 5 |
| C7 | 2,3-di-F | 3-CONHMe-4-NHMe | 387 | 5 |
| C8 | 2,3-di-F | 4-[CH ₂ CO(4-Me-Piperazin-1-yl)] | 441 | 5 |
| C9 | 2,3-di-F | 2-(Morpholin-4-yl) | 386 | 5 |
| C10 | 2,3-di-F | 3-[CH ₂ CO(Morpholin-4-yl)] | 428 | 5 |
| C11 | 2,3-di-F | 3-[CH ₂ CO(Piperidin-1-yl)] | 426 | 5 |

| | | | | |
|-----|-------------|---|------------------------|----|
| C12 | 2,3-di-F | 4-[CH ₂ CO(Piperidin-1-yl)] | 426 | 5 |
| C13 | 2,3-di-F | 4-[CH ₂ CONH(CH ₂) ₂ OH] | 402 | 5 |
| C14 | 2,3-di-F | 4-[CH ₂ CONMe ₂] | 386 | 5 |
| C15 | 2,3-di-F | 3-CONHMe-4-Cl | 392/394 | 5 |
| C16 | 2,3-di-F | 3-SO ₂ NH(CH ₂) ₂ OMe | 438 | 5 |
| C17 | 2,3-di-F | 3-SO ₂ NH _n Bu | 436 | 5 |
| C18 | 2,3-di-F | 3-COMe | 343 | 5 |
| C19 | 3-F | 3-CH ₂ CO ₂ H | 341 | 1 |
| C20 | 2,3-di-F | 3-NHCOMe | 358 | 5 |
| C21 | 2,3-di-F | 4-NHCOCF ₃ | 412 | 5 |
| C22 | 2,3-di-F | 2-Me | 315 | 5 |
| C23 | 2,3-di-F | 2-Me-4-F | 333 | 5 |
| C24 | 2,3-di-F | 2-Me-5-F | 333 | 5 |
| C25 | 2,3-di-F | 3-Me | 315 | 5 |
| C26 | 2,3-di-F | 2-SMe | 347 | 5 |
| C27 | 2,3-di-F | 3-CF ₃ -4-NH ₂ | 384 | 13 |
| C28 | 2,3-di-F | 3-CF ₃ -4-NHCOMe | 426 | 13 |
| C29 | 2,3,6-tri-F | 4-CH ₂ SO ₂ NHMe | 426 | 5 |
| C30 | 2,3,6-tri-F | 4-CH ₂ CH ₂ CONH ₂ | 390 | 5 |
| C31 | 2,3,6-tri-F | 3,5-di-F | 355 | 5 |
| C32 | 2,3,6-tri-F | 4-Me | 333 | 5 |
| C33 | 2,3,6-tri-F | H | 319 | 5 |
| C34 | 2,3-di-F | 3-[CH ₂ CONH(CH ₂) ₂ NMe ₂] | 429 | 5 |
| C35 | 2,3-di-F | 4-NH ₂ | 316 | 5 |
| C36 | 2,3-di-F | 3-NO ₂ | 344 [M-H] ⁻ | 11 |
| C37 | 2-Cl-5-F | 3-Cl | 351/353/355 | 5 |
| C38 | 2,3-di-F | 3-NH ₂ | 316 | 7 |
| C39 | 2,3-di-F | 2,3,4-tri-F | 355 | 11 |
| C40 | 2,3-di-F | 3-F-5-CF ₃ | 385 [M-H] ⁻ | 11 |

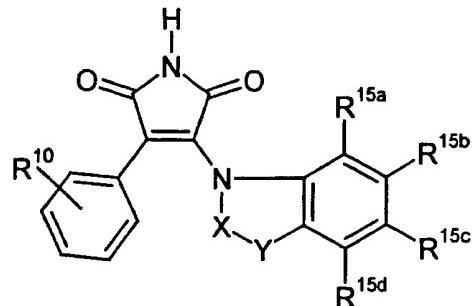
| | | | | |
|-----|---------------------|---|--|----|
| C41 | 2,3-di-F | 4-O(CH ₂) ₃ CO ₂ H | 403 | 1 |
| C42 | 2,3-di-F | 4-CH ₂ NHCO ₂ tBu | 428 [M-H] ⁻ | 1 |
| C43 | 3-CN | 4- <i>trans</i> -CH=CHCONH ₂ | 357 [M-H] ⁻ | 1 |
| C44 | 2,3-di-F | 4-NHCOCH ₂ OMe | 386 [M-H] ⁻ | 8 |
| C45 | 2,3-di-F | 4-NHCOCH ₂ NHCOMe | 415 | 8 |
| C46 | 2,3-di-F | 4-CH ₂ NHCO _n Pr | 400 | 8 |
| C47 | 2,3-di-F | 4-NHCOCH ₂ OH | 374 | 8 |
| C48 | 2,3-di-F | 3-NHCOCH ₂ OMe | 388 | 8 |
| C49 | 2,3-di-F | 4-NHCOCH ₂ CO ₂ tBu | 456 [M-H] ⁻ | 9 |
| C50 | 2,3-di-F | 3-NHCOCH ₂ NHCOMe | 413 [M-H] ⁻ | 8 |
| C51 | 3-CO ₂ H | H | 307 [M-H] ⁻ | 1 |
| C52 | 2,3-di-F | 4-NHCO _n Pr | 384 [M-H] ⁻ | 8 |
| C53 | 2,3-di-F | 4-NHCOCH ₂ CO ₂ H | 356 Fragment ion [M-CO ₂ H] ⁻ | 10 |
| C54 | 2,3-di-F | 4-CH ₂ NHCOCH ₂ OMe | 400 [M-H] ⁻ | 8 |
| C55 | 2,3-di-F | 4- CH ₂ NHCOCH ₂ NHCO Me | 427 [M-H] ⁻ | 8 |
| C56 | 3-CN | 4-(CH ₂) ₃ CO ₂ H | 374 [M-H] ⁻ | 1 |
| C57 | 3-CO ₂ H | 4-(CH ₂) ₃ CO ₂ H | 393 [M-H] ⁻ | 1 |
| C58 | 2,3-di-F | 3-CH ₂ NHCO ₂ tBu | 428 [M-H] ⁻ | 11 |
| C59 | 2,3-di-F | 4-CH ₂ NHCOCH ₂ OH | 386 [M-H] ⁻ | 8 |
| C60 | 3-CO ₂ H | 3,5-di-F | 343 [M-H] ⁻ | 1 |
| C61 | 3-CO ₂ H | 4-NHCOMe | 364 [M-H] ⁻ | 1 |
| C62 | 2,3-di-F | 3-NHCOCH ₂ OH | 372 [M-H] ⁻ | 8 |
| C63 | 2,3-di-F | 3-OH-4-NHCOMe | 374 | 12 |
| C64 | 2,3-di-F | 4- CH ₂ NHCOCH ₂ CO ₂ tBu | 470 [M-H] ⁻ | 9 |
| C65 | 3-CO ₂ H | 3-CH ₂ CONH ₂ | 364 [M-H] ⁻ | 1 |
| C66 | 2,3-di-F | 3-SO ₂ NH ₂ | 378 [M-H] ⁻ | 5 |
| C67 | 2,3-di-F | 3-CH ₂ NHCOCH ₂ OMe | 400 [M-H] ⁻ | 8 |

| | | | | |
|-----|----------------------|---|------------------------------------|---|
| C68 | 2,3-di-F | 3-CH ₂ NHCOCH ₂ NHCO Me | 429 | 8 |
| C69 | 2,3-di-F | 3-CH ₂ NHCOCH ₂ OH | 386 [M-H] ⁻ | 8 |
| C70 | 3-CH ₂ OH | H | 293 [M-H] ⁻ | 5 |
| C71 | 2,3-di-F | 4- <i>trans</i> -CH=CHCO ₂ H | 369 [M-H] ⁻ | 1 |
| C72 | 2,3-di-F | 4-NHCO(CH ₂) ₂ CONH ₂ | 413 [M-H] ⁻ | 8 |
| C73 | 2,3-di-F | 4-O(CH ₂) ₃ CONHMe | 416 | 5 |
| C74 | 3-CN | 4-NHCOMe | 345 [M-H] ⁻ | 5 |
| C75 | 3-CN | 4-CH ₂ SO ₂ NHMe | 395 [M-H] ⁻ | 5 |
| C76 | 2,3-di-F | 4-CH ₂ SO ₂ NMe ₂ | 420 [M-H] ⁻ | 5 |
| C77 | 3-CN | 3-CH ₂ CONH ₂ | 345 [M-H] ⁻ | 5 |
| C78 | 3-CH ₂ OH | 4-CH ₂ SO ₂ NHMe | 400 [M-H] ⁻ | 5 |
| C79 | 3-CH ₂ OH | 3,5-di-F | 329 [M-H] ⁻ | 5 |
| C80 | 2,3-di-F | 4-[CH ₂ -(1,3-thiazolidine-2,4-dion-5-yl)] | 430 | 5 |
| C81 | 2,3-di-F | 3-CH ₂ CH ₂ CO ₂ H | 373 | 1 |
| C82 | 2,3,6-tri-F | 4-CH ₂ CH ₂ CH ₂ CO ₂ H | 403 [M-H] ⁻ | 1 |
| C83 | 2-F-3-Cl | 4-CH ₂ CH ₂ CH ₂ CO ₂ H | 401/403 [M-H] ⁻ | 1 |
| C84 | 2-F-3-Cl | 3,5-di-F | 351/353 [M-H] ⁻ | 5 |
| C85 | 2,3-di-F | 4-OH | 315 [M-H] ⁻ | 5 |
| C86 | 2,3,6-tri-F | 3,5-di-Cl-4-OH | 401/403/405 [M-H] ⁻ | 5 |
| C87 | 2-F-3-Cl | 3,5-di-Cl-4-OH | 399/401/403/405 [M-H] ⁻ | 5 |
| C88 | 2-Cl-3-F | 3,5-di-Cl-4-OH | 399/401/403/405 [M-H] ⁻ | 5 |
| C89 | 2-Cl-3-F | 4-(CH ₂) ₃ CO ₂ H | 401/403 [M-H] ⁻ | 1 |
| C90 | 2-Cl-3-F | 3,5-di-F | 351/353 [M-H] ⁻ | 5 |
| C91 | 4-NO ₂ | 3,5-di-F | 344 [M-H] ⁻ | 5 |
| C92 | 4-I | 3,5-di-F | 425 [M-H] ⁻ | 5 |

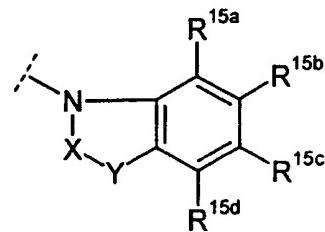
| | | | | |
|------|----------|---|-----------------------------|----|
| C93 | 2,3-di-F | 3-F-4-OCH ₂ CO ₂ H | 393 | 1 |
| C94 | 2,3-di-F | 4-NHCOCO ₂ H | 342 [M-H-CO ₂]- | 1 |
| C95 | 2-Cl | 3-[CH ₂ -(1,3-thiazolidine-2,4-dion-5-yl)] | 428/430 | 5 |
| C96 | 2,3-di-F | 3-Me-4- <i>trans</i> -CH=CHCO ₂ H | 383 [M-H]- | 1 |
| C97 | 4-NHCOMe | 3,5-di-F | 357 [M]- | 19 |
| C98 | 2,3-di-F | 3-CH ₂ CONHNHCOMe | 415 | 17 |
| C99 | 2,3-di-F | 4-(CH ₂) ₄ NHCOMe | 414 | 5 |
| C100 | 2,3-di-F | 4-(CH ₂) ₄ NHSO ₂ Me | 448 [M-H]- | 5 |
| C101 | 2,3-di-F | 3-CH ₂ NHSO ₂ Me | 406 [M-H]- | 5 |
| C102 | 2,3-di-F | 4-CH ₂ CH ₂ P(O)(OEt)OH | 435 [M-H]- | 1 |
| C103 | 2,3-di-F | 4-CH ₂ CH ₂ SO ₂ NH ₂ | 407 [M]- | 5 |
| C104 | 2,3-di-F | 3-CH ₂ SO ₂ NH ₂ | 392 [M-H]- | 1 |
| C105 | 2,3-di-F | 3-CH ₂ CONHOMe | 386 [M-H]- | 17 |
| C106 | 2,3-di-F | 3-CH ₂ CONHOH | 372 [M-H]- | 21 |
| C107 | 2,3-di-F | 4- <i>trans</i> -CH=CHCONHOMe | 400 | 1 |
| C108 | 2,3-di-F | 4-CH ₂ NH ₂ | 330 | 20 |
| C109 | 2,3-di-F | 3-CH ₂ NH ₂ | 330 | 20 |

Table D

5 Encompassing compounds of general formula (Z-5), wherein group R² of formula (I) is a phenyl ring, optionally substituted by one or more substituents R¹⁰ and the moiety - NR¹R³ of formula (I) represents a heterocyclyl moiety of general formula (Z-6), optionally substituted by substituents R^{15a}, R^{15b}, R^{15c} and R^{15d} and substituents R¹⁰, R^{15a}, R^{15b}, R^{15c}, R^{15d} and X-Y are listed in Table D.



(Z-5)



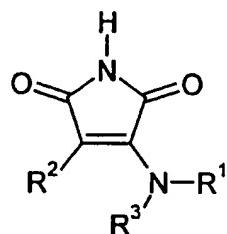
(Z-6)

10

| Example No. | R ¹⁰ | R ^{15a} | R ^{15b} | R ^{15c} | R ^{15d} | X-Y | [M+H] ⁺ Observed; (Unless [M] ⁻ or [M-H] ⁻ are Indicated) | For Procedure See Example No. |
|-------------|-----------------|------------------|------------------|------------------|------------------|---|--|-------------------------------|
| D1 | 2,3-di-F | H | H | H | H | CH(CH ₂ OH)C H ₂ (S)-Isomer | 357 | 5 |
| D2 | 2,3,6-tri-F | H | H | H | H | (CH ₂) ₂ | 345 | 5 |
| D3 | 2,3-di-F | H | H | H | H | (CH ₂) ₃ | 341 | 5 |
| D4 | 3,5-di-Me | H | H | H | H | (CH ₂) ₃ | 333 | 5 |
| D5 | 2-Cl | H | H | H | H | (CH ₂) ₃ | 339/341 | 11 |
| D6 | 2,3-di-F | H | H | H | H | CH(CH ₂ OMe) CH ₂ | 371 | 14 |

Table E

Encompassing compounds of general formula I, and substituents R¹ R² and R³ are listed
 5 in Table E.



(I)

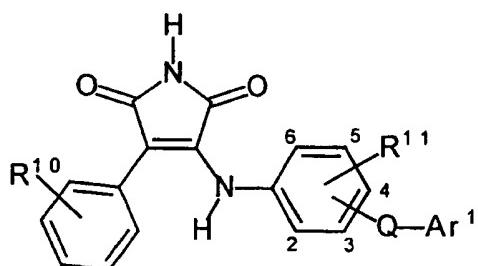
10

| Example No. | R ¹ | R ² | R ³ | [M+H] ⁺ Observed; (Unless [M] ⁻ or [M-H] ⁻ are Indicated) | For Procedure See Example No. |
|-------------|--|----------------|----------------|---|---|
| E1 | 2-[(CH ₂) ₂ CO ₂ H]-Pyridin-5-yl | 2,3-di-F-Ph | H | 374 | 6 |
| E2 | 2-[(CH ₂) ₃ CN]-3-Me-Pyridin-5-yl | 2,3-di-F-Ph | H | 383 | 6 |
| E3 | 2-Me-Pyridin-3-yl | 2,3-di-F-Ph | H | 316 | 6 |
| E4 | 2-[(CH ₂) ₃ CN]-3-(CO ₂ Et)-Pyridin-5-yl | 2,3-di-F-Ph | H | 441 | 6 |
| E5 | 2-[(CH ₂) ₄ CO ₂ H]-Pyridin-5-yl | 2,3-di-F-Ph | H | 402 | 6 |
| E6 | 2-[(CH ₂) ₃ CN]-Pyridin-3-yl | 2,3-di-F-Ph | H | 369 | 6 |
| E7 | 2-(OPh)-Pyridin-5-yl | 2,3-di-F-Ph | H | 394 | 15 |

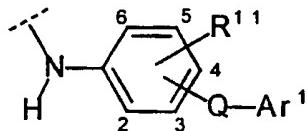
Table F

5 Encompassing compounds of general formula (Z-7), wherein group R^2 of formula (I) is a phenyl ring, optionally substituted by one or more substituents R^{10} and the moiety NR^1R^3 of formula (I) is represented by a moiety of general formula (Z-8), optionally substituted by one or more substituents R^{11} . Q represents a linking moiety and Ar^1 represents an aromatic heterocyclic group as hereinbefore defined. The positions of substitution of R^{10} and Q are defined with reference to formula (Z-8) and the values of R^{10} , R^{11} , Q and Ar^1 are listed in Table F.

10



(Z- 7)



(Z- 8)

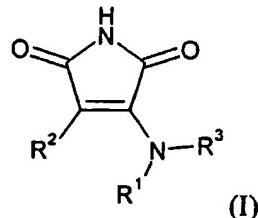
| Example No. | R ¹⁰ | R ¹¹ | Q | Ar ¹ | [M+H] ⁺ Observed; (Unless [M] ⁻ or [M-H] ⁻ are Indicated) | For Procedure See Example No. |
|-------------|-----------------|-----------------|--|------------------------|--|-------------------------------|
| F1 | 2,3-di-F | H | 3-[bond] | 5-Oxazolyl | 368 | 5 |
| F2 | 2,3-di-F | H | 4-[NHCO(CH ₂) ₂] | 3-Pyridinyl | 449 | 8 |
| F3 | 2,3-di-F | H | 4-[bond] | 5-Me-2-Oxazolyl | 382 | 5 |
| F4 | 2,3-di-F | H | 4-[bond] | 2-Me-4-Oxazolyl | 382 | 5 |
| F5 | 2,3-di-F | H | 4-[bond] | 6-Me-Benzothiazol-2-yl | 448 | 5 |

| | | | | | | |
|-----|----------|------|--|---------------------------------|------------|----|
| F6 | 2,3-di-F | H | 4-[O] | 3-Pyridinyl | 392 [M-H]- | 15 |
| F7 | 2,3-di-F | 4-OH | 3-[bond] | Benzothiazol-2-yl | 450 | 14 |
| F8 | 2,3-di-F | H | 3-[CH ₂ CO NH] | Quinolin-3-yl | 485 | 17 |
| F9 | 2,3-di-F | H | 4-[bond] | 3-Me-1,2,4-Oxadiazol-5-yl | 381 [M-H]- | 5 |
| F10 | 2,3-di-F | H | 3-[CH ₂ CO NH] | 2-Me-Pyridin-3-yl | 449 | 17 |
| F11 | 2,3-di-F | H | 3-[CH ₂ CO NH] | 5-Me-Pyridin-3-yl | 449 | 17 |
| F12 | 2,3-di-F | H | 3-[CH ₂ CO NH] | 2-OMe-Pyridin-5-yl | 465 | 17 |
| F13 | 2,3-di-F | H | 3-[CH ₂ CO NH] | Pyridin-3-yl | 435 | 17 |
| F14 | 2,3-di-F | H | 3-[CH ₂ CO 2CH ₂] | 3-NH ₂ -Pyridin-2-yl | 465 | 22 |
| F15 | 2,3-di-F | H | 4-[O(CH ₂) ₂ NMe] | Pyridin-2-yl | 451 | 1 |
| F16 | 2,3-di-F | H | 4-[OCH ₂] | Pyridin-3-yl | 408 | 1 |
| F17 | 2,3-di-F | H | 3-[CH ₂ CO NH] | Pyrimidin-4-yl | 436 | 17 |
| F18 | 2,3-di-F | H | 3-[CH ₂ CO NH] | Pyrazin-2-yl | 436 | 17 |
| F19 | 2,3-di-F | H | 4-[O] | Pyridin-2-yl | 392 [M-H]- | 5 |
| F20 | 2,3-di-F | H | 4-[bond] | 2-OH-Pyrimidin-5-yl | 393 [M-H]- | 5 |

| | | | | | | |
|-----|----------|---|--------------|--|------------|---|
| F21 | 2,3-di-F | H | 4-[bond] | 5-Me-4,5-dihydro-2H-pyridazin-3-on-6-yl | 409 [M-H]- | 5 |
| F22 | 2,3-di-F | H | 4-[bond] | 2,5-di-Me-4,5-dihydro-2H-pyridazin-3-on-6-yl | 423 [M-H]- | 5 |
| F23 | 2,3-di-F | H | 4-[bond] | 1H-Pyrazol-3-yl | 365 [M-H]- | 5 |
| F24 | 2,3-di-F | H | 4-[SCH2] | 1H-Imidazol-4-yl | 413 | 5 |
| F25 | 2,3-di-F | H | 3-[CH2SO2NH] | Pyridin-3-yl | 471 | 1 |
| F26 | 2,3-di-F | H | 4-[bond] | 2-OMe-Pyrazin-5-yl | 409 | 5 |
| F27 | 2,3-di-F | H | 4-[bond] | 1H-Pyrazin-2-on-5-yl | 395 | 5 |
| F28 | 2,3-di-F | H | 4-[bond] | 5,6-Dihydro-4H-[1,3,4]-Oxadiazin-5-on-2-yl] | 397 [M-H]- | 5 |
| F29 | 2,3-di-F | H | 4-[bond] | 4,5-dihydro-2H-pyridazin-3-on-6-yl | 395 [M-H]- | 5 |
| F30 | 2,3-di-F | H | 4-[bond] | 2H-pyridazin-3-on-6-yl | 393 [M-H]- | 5 |

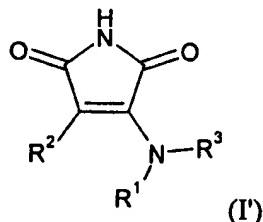
Claims

1. A method for the treatment of conditions associated with a need for inhibition of GSK-3, such as diabetes, conditions associated with diabetes, chronic neurodegenerative 5 conditions including dementias such as Alzheimer's disease, neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and manic depression, hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, inflammation and immunodeficiency, which method comprises the administration of a pharmaceutically effective, non-toxic amount of a compound of formula (I):



- 15 or a pharmaceutically acceptable derivative thereof,
wherein;
- R¹ is a substituted or unsubstituted carbocyclic or heterocyclic aromatic ring, which ring may be fused to a substituted or unsubstituted carbocyclic or heterocyclic aromatic or non-aromatic ring;
- 20 R² is a substituted or unsubstituted carbocyclic or heterocyclic aromatic ring, which ring may be fused to a substituted or unsubstituted carbocyclic or heterocyclic aromatic ring, with the proviso that R² is not 3-indolyl or a fused-ring derivative of 3-indolyl;
- R³ is hydrogen, or,
- 25 R¹ and R³ together with the nitrogen atom to which they are attached form a fused substituted or unsubstituted heterocyclic ring;
to a human or non-human mammal in need thereof.

2. A compound of formula (I')

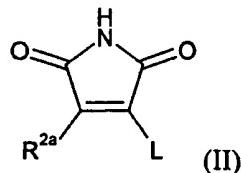


- 30 wherein;
- R¹, R², and R³ are as defined in formula (I) in claim 1, with the proviso that formula (I') does not include the following compound:

3-phenylamino-4-phenyl-1H-pyrrole-2,5-dione.

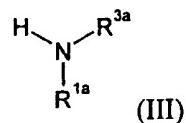
3. A process for the preparation of a compound of formula (I'), which process comprises reaction of a compound of formula (II)

5



wherein;

10 R^{2a} is as defined for R^2 in formula (I) in claim 1 and L is a leaving group, with a compound of formula (III)



wherein;

15 R^{1a} and R^{3a} are as defined for R^1 and R^3 respectively in formula (I) in claim 1, and thereafter, if required, carrying out one or more of the following optional steps:

- (i) converting a compound of formula (I') to a further compound of formula (I');
- (ii) removing any necessary protecting group;
- (iii) preparing an appropriate derivative of the compound so formed.

20

4. A compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable derivative thereof, for use as an inhibitor of glycogen synthase kinase-3, and especially for use in the treatment of conditions associated with a need for the inhibition of GSK-3, such as diabetes, conditions associated with diabetes, chronic

25 neurodegenerative conditions including dementias such as Alzheimer's disease, neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and manic depression, hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, inflammation and immunodeficiency.

30

5. Use of a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable derivative thereof, for the manufacture of a medicament for the treatment of conditions associated with a need for the inhibition of GSK-3, such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including

35 dementias such as Alzheimer's disease, neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and manic depression, hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, inflammation and immunodeficiency.

6. A compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable derivative thereof, for use as an active therapeutic substance.
- 5 7. A pharmaceutical composition which comprises a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/03687

A. CLASSIFICATION OF SUBJECT MATTER

| | | | | | |
|-------|-------------|------------|------------|------------|-------------|
| IPC 7 | C07D207/44 | C07D401/12 | C07D417/12 | C07D403/12 | C07D413/12 |
| | C07D409/12 | C07D407/12 | C07D403/04 | C07D401/04 | A61K31/4015 |
| | A61K31/4025 | A61P3/10 | | | |

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

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Information on patent family members

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